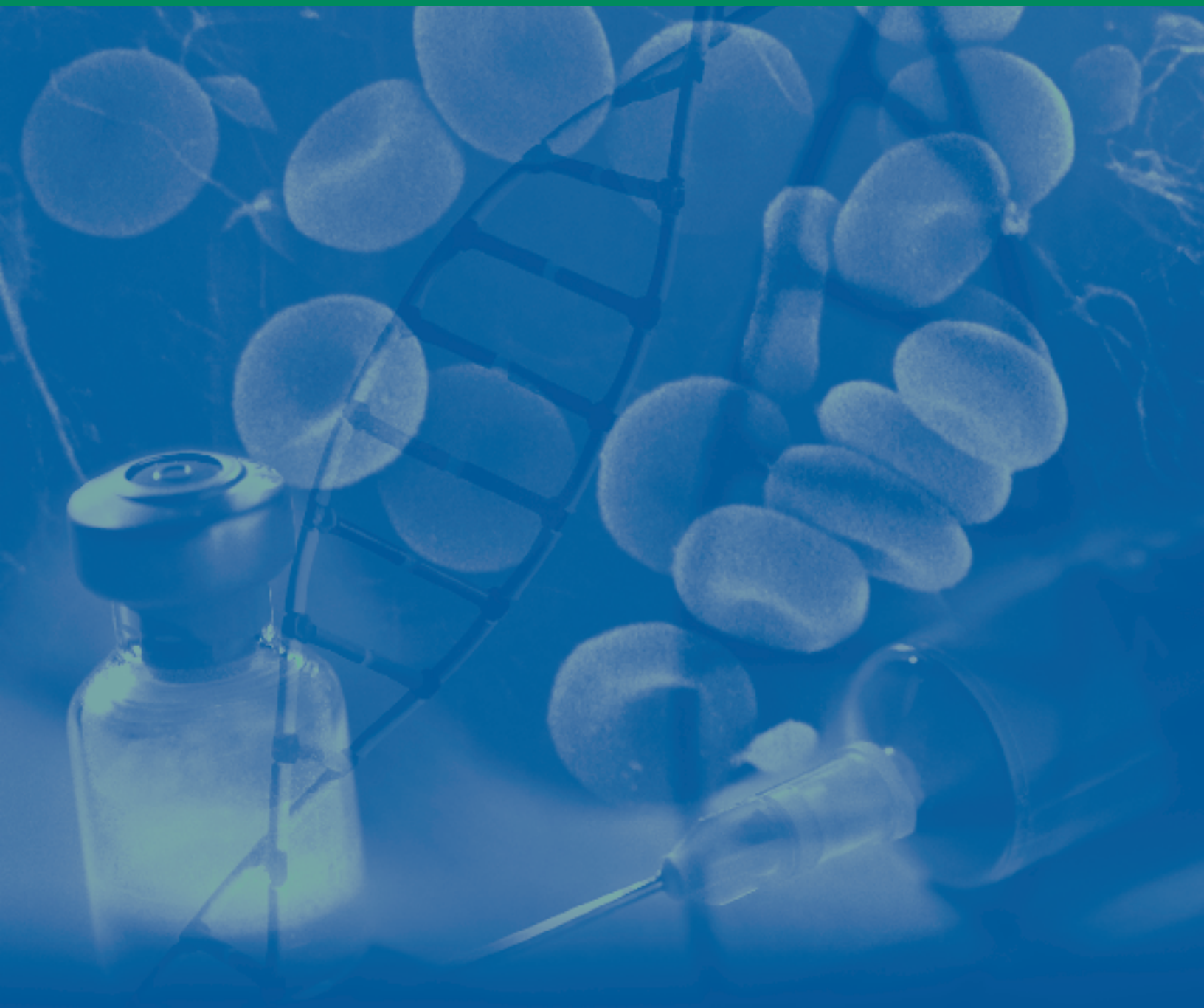
FY 2005 ANNUAL REPORT

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH



Innovative Technology Advancing Public Health

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VISION AND MISSION

Vision

The Center for Biologics Evaluation and Research (CBER) uses sound science and regulatory expertise to:

- Protect and improve public and individual health in the United States and, where feasible, globally;
- Facilitate the development of, approval of, and access to safe and effective products and promising new technologies; and
- Strengthen CBER as a preeminent regulatory organization for biologics.

Mission

To ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through our mission, we also help to defend the public against the threats of emerging infectious diseases and bioterrorism.

In fulfilling our mission as a Center in the U.S. Food and Drug Administration, we apply the following principles with the highest ethical standards and integrity:

- Develop, maintain, and support a high-quality and diverse workforce;
- Ensure compliance with laws and regulations through review, education, surveillance, and enforcement; and
- Conduct research as an essential element of science-based decision-making.

Center for Biologics Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

A MESSAGE FROM THE DIRECTOR

June 2006

Dear Colleagues in the Biologics Community:

I am pleased to provide the ninth annual report from the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER). This report provides highlights from CBER's activities during Fiscal Year (FY) 2005 and addresses current initiatives. The Center is responsible for ensuring the safety and efficacy of a wide range of biologic products including vaccines and allergenic products, blood, blood products and devices and tests used in transfusion, and human tissues, cell and gene therapies. The products regulated by CBER touch the lives of people everyday. They are also critical in public health preparedness – protecting our health and welfare against emerging infectious diseases and terrorism. FDA's strategic framework lays out an action plan and goals to accomplish FDA's primary mission to protect and promote the public health. These goals cut across all of FDA's Centers, and many of the goals include extensive inter-Center collaboration. CBER's FY 2005 annual report is organized within these four critical goals/areas. CBER embraces each goal and is working closely with other organizations to achieve them. The four goals are:

1. Increasing access to innovative products and technologies to improve health.
2. Enhancing patient and consumer protection and empowering them with better information about regulated products.
3. Improving product quality, safety, and availability through better manufacturing and product oversight.
4. Transforming FDA business operations, systems, and infrastructure to support FDA's mission in the 21st Century.

In each of these areas, as documented in this report, CBER has made substantial progress. CBER continues to meet or exceed the performance goals in the Prescription Drug User Fee Act (PDUFA) III. In addition, through improvements in training, management, and the hard work and commitment of reviewers, CBER has made substantial improvements in the review of device submissions, and has met or exceeded the performance goals in the Medical Device User Fee and Modernization Act (MDUFMA). Our successes in accomplishing thorough but timely scientific review of biological products and related devices have meant that more safe and effective products are reaching those in need more efficiently and rapidly, and combined with aggressive monitoring of product quality and safety, have helped to keep needed vaccines, tissues and blood products both safe and available.

CBER continues to accomplish its highest priority public health objectives and meet exceptional challenges through collaborative, innovative and, where needed, transformational actions. We have worked together to increase our outreach and to put in place innovative approaches to product evaluation, access and safety. For example, in response to the need for additional influenza vaccine capacity for both

annual and pandemic preparedness, CBER developed a pathway for accelerated approval based on a surrogate marker likely to predict clinical benefit, engaged the National Institutes of Health's (NIH) National Institute of Allergy and Infectious Disease (NIAID) in assisting with needed clinical studies, and conducted highly proactive assessments of manufacturing and clinical data. As a result, an additional influenza vaccine became U.S. licensed in a very short time-span to help meet needs for vaccine in the 2005-2006 season. We partnered with the United Kingdom (UK) regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA), to help remediate some industry manufacturing problems resulting in improved access to these vaccines. CBER has also defined pathways for pandemic vaccine preparedness for both new and existing technologies, and has interacted extensively with Department of Health and Human Services (DHHS) colleagues, industry, and global regulatory partners. The Center was re-designated as a Pan American Health Organization (PAHO)/ World Health Organization (WHO) Collaborating Center for Biological Standardization, a standing that reflects the important leadership role of CBER in global biologics standards and the significance the Center places on its engagement with WHO and in addressing global public health needs and opportunities. We proposed and are co-sponsoring with WHO a global regulators meeting to help facilitate communication, harmonization and quality in pandemic flu vaccine development.

Getting ahead of the curve on new technologies and emerging threats and collaborating with colleagues both inside and outside of FDA to find needed solutions adds value and effectiveness to all that we do. Gene and cell therapies offer the promise of cure for many diseases yet also raise unique challenges. These include for example the possibility of late adverse effects related to the therapy, and the persistence of the genes and/or cells in treated patients. CBER has helped provide standards and define needed pathways for development of these promising therapies. Among the many examples of our approach, CBER has activley sought input from academia, product developers and others in providing needed guidance on long-term follow up of gene therapies, and working with WHO to foster international consistency. We have worked with our colleagues in the FDA's Center for Devices and Radiological Health (CDRH) to set up a pilot joint Tissue Engineering Review Team to define and provide new regulatory pathways and approaches for these promising, yet complex, products. Similarly, we are working closely with colleagues in FDA's Center for Drug Evaluation and Research (CDER) and with the National Cancer Institute (NCI) to strengthen and coordinate both the science and training base and the review of Oncology products, an effort to bring safe and effective products to cancer patients as quickly as possible. We continue to interact intensively with DHHS, Department of Defense (DoD), and industry on a broad array of projects to help make our nation better prepared for pandemic influenza, emerging infectious diseases and the threats of biological, chemical and radiological/nuclear terrorism. These activities have included licensing important new products for treating complications of smallpox vaccine, organizing and attending numerous workshops to help advance the development of needed products, and providing other forms of guidance to facilitate the product development and manufacturing needed to help support Project BioShield and other critical priorities.

We have developed and implemented the new human tissue regulatory framework and put together an interdisciplinary Tissue Safety Team, combining manufacturing, clinical and epidemiologic expertise, working closely with the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA), to monitor safety and further develop the needed activities to effectively protect tissues against infectious disease threats. We are extending the Tissue Safety Team model to our other product areas, a model involving interdisciplinary teams working together to detect and analyze possible adverse events, as well as to address product manufacturing and quality issues, and to respond to emerging threats.

Our proactive and collaborative approach to emerging infectious diseases has been exemplified by the continued success of implementing West Nile virus (WNV) screening and the removal of more than 1,000 infected units of blood prior to their potential use. As a result of the application of quality approaches and advanced technologies, our blood and plasma product supply has become safer than ever in history – but we must remain vigilant. Consistent with the Agency's Good Manufacturing Practices Initiative, and in an effort to accomplish the most effective use of limited resources, CBER has developed new risk-based compliance programs and training for the products we regulate, for example, plasma and blood products. We have conducted outreach on GMPs, with a significant new focus on taking a preventive approach to challenges specific to the vaccine industry.

In summary, challenging times have called for continued hard work, strong leadership, and the support of an outstanding staff. These factors have led to remarkable accomplishments and contributions to the FDA and DHHS missions.

In the coming year, our major priorities, which also support the priorities of the FDA and Acting Commissioner Andrew von Eschenbach and of HHS Secretary Michael Levitt, will include:

- Pandemic influenza, emerging infectious diseases, and counterterrorism preparedness and response, including support of the effort to develop enhanced influenza vaccine supplies and new technologies and new medical countermeasures against terrorism threats;
- Preparedness to assure continuity of mission critical operations in the face of a pandemic or of natural or deliberate catastrophes;
- Enhanced product safety activities, including interdisciplinary team approaches and increased use of information technology for problem detection and analysis, and to guide prevention efforts;
- Collaborative and prioritized management and application of our laboratory, epidemiologic and statistical scientific resources to support the Critical Path: providing scientific tools, models and guidance to industry to facilitate development, evaluation and quality of innovative products for 21st Century medicine and public health;
- Use of sound management and information technology to continue to support and improve the review process and its efficiency; and
- Increased outreach and use of risk based approaches to manufacturing quality and its assessment.

Despite many challenges, we are optimistic and see tremendous opportunities such as vaccines that will prevent or treat cancers, cell and gene therapies that will treat or correct diseases, and a robust and safe supply of vaccines, blood and tissues, critical in supporting today's medical care and our nation's preparedness.

While CBER plays a unique role in evaluating product safety and effectiveness, meeting these challenges and opportunities requires concerted and collaborative efforts and the best ideas, wherever they come from. All of us at CBER take these responsibilities seriously and appreciate your continuing support and input – I personally welcome your feedback and ideas. We look forward to working with all of you in the coming year. The public, both well and sick, and the nation, depends on all of us.

Sincerely,

Jesse L. Goodman, M.D., M.P.H.
Director
Center for Biologics Evaluation and Research

OUR PRODUCTS

Blood and Blood Products

The FDA is responsible for ensuring the safety of the nation's blood supply by minimizing the risk of infectious disease transmission and other hazards, while facilitating the maintenance of an adequate supply of blood and blood products. CBER regulates the collection of blood and blood components that are used for transfusion or for the manufacture of related products, such as clotting factors and immunoglobulin concentrates, and establishes product standards. CBER also regulates products used to prepare blood products, including products such as cell separation devices, blood collection containers, and blood donor tests to screen for human immunodeficiency virus (HIV) and other infectious diseases. CBER develops and enforces quality standards, monitors, analyzes and, as needed, acts on reports of biological product deviations, including unexpected or unforeseeable events in manufacturing as well as adverse clinical events.

For example, FDA encouraged the development of highly sensitive nucleic acid tests (NAT) for HIV-1 and hepatitis C virus (HCV). These tests are now FDA-approved and recommended for use in blood screening to reduce the risk of transmission of these agents. To standardize the performance of these tests, CBER developed needed lot release reagents. The FDA also encouraged the development of NAT tests for West Nile virus (WNV) in response to the epidemic in the United States. Close coordination with other U.S. Public Health Service (PHS) agencies, device manufacturers, and blood establishments resulted in investigational WNV tests being developed and utilized in blood establishments within eight months of recognition of this new risk, with the goal of licensure for these tests.

Over a period of years, FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products. Blood donors are asked specific questions and review educational materials about risk factors that could indicate possible infection with a transmissible disease. This upfront donor screening helps to reduce risk from infectious agents by identifying potentially high-risk donors prior to testing, and is especially important in the absence of donor screening tests.

FDA also facilitates the development and implementation of sensitive tests to detect infectious agents in blood. To further enhance blood safety, FDA requires blood centers to maintain lists of donors with positive tests or significant risk factors for infectious diseases that can be transmitted by blood to prevent the use of unsuitable collections. In addition, FDA has significantly increased its oversight through inspections of blood manufacturing facilities.

Vaccines and Vaccine Safety

CBER regulates vaccine products. Many of these are pediatric vaccines that have contributed to the dramatic reduction of dreaded childhood diseases such as polio and measles. Newer vaccines under development offer the promise to prevent emerging infectious diseases, such as pandemic influenza viruses and severe acute respiratory syndrome (SARS), and even some cancers, such as cervical cancer, a major killer of women worldwide. Vaccines must undergo rigorous review of laboratory and clinical data to ensure their safety, efficacy, purity and potency. FDA also reviews additional studies after some vaccines are approved to further evaluate their safety and effectiveness, for example, in broader population groups. Both before and after a vaccine is licensed, FDA also inspects vaccine manufacturing facilities to help ensure continued high-quality production.

The U.S. Centers for Disease Control and Prevention (CDC) and CBER jointly manage the Vaccine Adverse Event Reporting System (VAERS), a cooperative program for vaccine safety. VAERS is a post-marketing safety surveillance program that collects information about adverse events (suspected side effects) potentially related to vaccination, reported after the administration of U.S.-licensed vaccines. In collaboration with CDC, state health departments and other partners, CBER uses VAERS to monitor vaccine adverse event reports for possible indicators of vaccine safety concerns.[1-4]

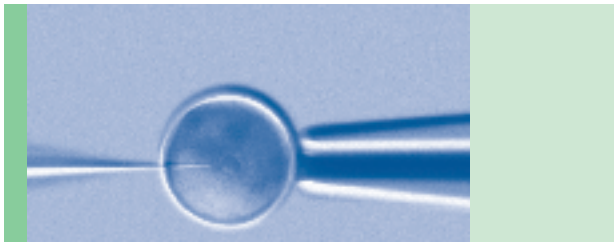
Cellular and Gene Therapies

CBER regulates cellular and gene therapies and cancer vaccines. Somatic cells, vectors expressing needed gene products, or genetically manipulated cells offer the promise of harnessing the power of different cell types to fight disease, restore normal function, repair injuries, replace lost cells, or regenerate failing organs.

CBER is aware of both the promise of gene therapy and its potential to cause serious adverse events. The Center is striving to ensure that gene therapy products are as safe as possible while studies of these promising therapies continue, particularly for patients in desperate need of better treatment for chronic diseases. The FDA works closely with the National Institutes of Health (NIH), academia, and industry in these efforts. For example, FDA and the NIH have collaboratively developed a Web-accessible database on human gene transfer—Genetic Modification Clinical Research Information System (GeMCRIS). The system enables faster reporting of adverse events in human gene transfer trials and is a unique public information resource. The system provides information to the public directly via the Internet (see www.gemcris.od.nih.gov) and improves the government's ability to monitor adverse events in gene therapy.

Manufacturers of gene and cellular therapy products must study their products adequately in the laboratory for safety before beginning any studies in humans under an investigational new drug (IND) application. Like all biological products, gene and cellular therapies need to meet statutory and regulatory requirements for safety, purity, and potency before the products can be licensed for commercial distribution in the United States. While CBER has received no gene therapy biological license applications (BLA) to date, CBER has received more than 489 gene therapy INDs, and is currently overseeing approximately 249 active studies. CBER received 1,089 investigational files for somatic cellular therapies through FY 2005, and approximately 400 are active. To date, there is one licensed cellular therapy product. In addition, there were 40 INDs for xenotransplantation products, and approximately 13 were active by the end of FY 2005.

CBER has provided proactive scientific and regulatory guidance in areas of novel product development. The Center communicates regulatory expectations and encourages dialogue on cutting-edge product development to help define the best scientific approaches and reduce product development time and risk. Focusing on how best to evaluate essential issues of safety and efficacy, CBER is able to facilitate product development and avoid unnecessary regulatory burdens while protecting human study subjects. In addition, our involvement in broad public interactions helps CBER and product developers address difficult issues involving the risks and benefits of research to develop novel genetic and cellular therapy products.

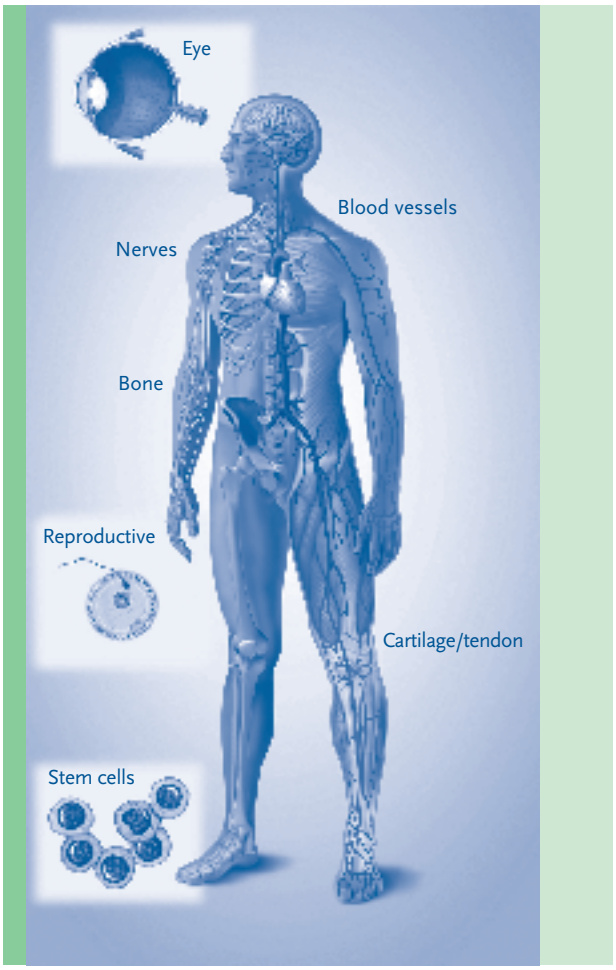


Tissues

Tissue transplantation is a rapidly growing industry. The number of musculoskeletal tissue transplants increased from approximately 350,000 in 1990 to more than one million in 2004. CBER is responsible for regulating many different types of human tissue and cells that are transplanted during various types of medical procedures, such as skin replacement following severe burns, tendons and ligaments used to repair injuries, bone replacement, and corneas used to restore eyesight. The transplantation of human tissues presents unique safety challenges, in particular the risks of transmitting infectious diseases from donor to recipient and of contamination of tissues during processing. These risks can be significantly reduced, but not completely eliminated.

Since 1993, CBER has required tissue establishments to screen and test donors. Since 1997, CBER has required tissue establishments to prepare, validate, and follow written procedures to prevent contamination and cross-contamination during processing. In response to the increased use, role, and complexity of tissue transplants and the recognition of threats to tissue safety, FDA developed and is now implementing a comprehensive new framework for the regulation of human cells, tissues, and cellular and tissue-based products. The

new framework promotes the use of the most up-to-date tools and methods to reduce risks of infectious disease transmission and contamination. In addition to extending the scope of FDA authority to include a broader range of tissues (e.g., hematopoietic stem cells and reproductive tissues, the latter covered primarily for donor eligibility and testing issues), the new regulations encourage a comprehensive yet flexible approach to quality in manufacturing throughout the entire process, from donor assessment to the final product, including adverse event reporting. CBER conducted extensive outreach and sought stakeholder input throughout the process. CBER recognizes that the implementation of the new regulations, along with the continued evolution of the science, will pose many challenges. CBER is committed to continuing to conduct outreach to enhance the quality and performance of both the industry and the Agency. These efforts should result in enhanced safety and public confidence.



Xenotransplantation

CBER also regulates products used in xenotransplantation, which is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: a) live cells, tissues, or organs from a nonhuman animal source; or, b) human body fluids, cells, tissues, or organs that have had any contact with live nonhuman animal cells, tissues, or organs. Xenotransplantation offers the promise of providing needed organs and tissues to thousands of individuals who await transplants of scarce human organs. It holds the potential for the treatment of a wide range of conditions and disorders including diabetes, Parkinson's disease, and other diseases involving tissue destruction and organ failure.

Currently, the demand for human organs for clinical transplantation far exceeds the supply. While xenotransplantation's potential benefits are considerable, it raises a number of complex scientific and public health challenges, most notably the risk of transmission of infectious diseases from animals to humans, and the failure of such transplants due to rejection. CBER's continued careful oversight and caution are critical to protecting public health while exploring the vast potential of these experimental therapies.

In 1998, CBER initiated the Xenotransplantation Action Plan for the purpose of providing a comprehensive approach for the regulation of xenotransplantation. The plan addresses the potential public health safety issues associated with xenotransplantation and the need to provide guidance to sponsors, manufacturers, and investigators regarding xenotransplantation product safety and clinical trial design and monitoring.[5]

CBER also remains significantly involved in international activities for the safety and regulation of xenotransplantation products.

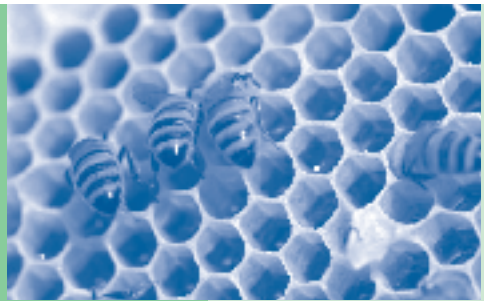
Devices

CBER regulates many medical devices used in the collection, processing, testing, manufacture, and administration of blood, blood components, and human cells, tissues and cellular and tissue based products. The Center also regulates HIV and other infectious disease test kits used to screen donor blood, blood components, and cellular and tissue product donors, as well as HIV tests used to diagnose, treat, and monitor therapy in persons with HIV and autoimmune deficiency syndrome (AIDS). CBER collaborates closely with FDA's Center for Devices and Radiological Health (CDRH) and the Office of Combination Products in the regulation of these medical devices and of combination products that combine cellular or gene therapies with innovative and promising approaches to disease treatments. The Center also has leveraged its resources by working with the National Toxicology Program, a joint FDA-NIH venture,

to evaluate safety issues associated with materials used in blood collection and transfusion devices.

Allergenics

There are currently two types of allergenic products licensed for use: allergen patch tests and allergenic extracts. Allergen patch tests are diagnostic tests applied to the surface of the skin. Patch tests are used by physicians to determine the specific causes of contact dermatitis, and are manufactured from natural substances or chemicals such as nickel, rubber, and fragrance mixes that are known to cause contact dermatitis. Allergenic extracts are used for the diagnosis and treatment of allergic diseases such as allergic rhinitis ("hay fever"), allergic sinusitis, allergic conjunctivitis, bee venom allergy, and food allergy. CBER has been proactive in evaluating novel technological approaches for improving allergenic product development and standardization, as well as characterizing these complex biological products.[6]



Some allergenic extracts are currently standardized, while others are non-standardized. Prior to release, standardized allergenic extracts are compared to U.S. reference standards for potency. CBER maintains these reference standards and distributes them to manufacturers. There are currently 19 standardized allergenic extracts. The Center has been updating technologic approaches to improve the safety, efficacy, and standardization of allergenic products. For example, in 2003, CBER initiated a study to examine the levels of endotoxin in allergenic extracts in order to help improve product quality and consistency. Endotoxins, which are derived from bacteria, are commonly found in allergenic extracts. The study results show the presence of variable amounts of endotoxins in some allergenic extracts. Further evaluation is underway to understand possible effects of the presence of variable amounts of endotoxins on the performance of and reactions to these extracts.

INCREASING ACCESS TO INNOVATIVE PRODUCTS AND TECHNOLOGIES TO IMPROVE HEALTH

Initiatives to Strengthen, Diversify, and Increase Capacity of Influenza Vaccine and Biologics Technologies

CBER is responsible for the regulation and oversight of vaccines in the United States. Vaccines are among our most important and cost-effective medical interventions, preventing disease in those who receive them and reducing the spread and risk of infections through our communities. The safety, effectiveness, and availability of vaccines are among CBER's highest priorities and we work closely with DHHS, CDC, NIH, and manufacturers in addressing this important area of public health preparedness.

The 2004-2005 Influenza Season

Influenza vaccine is unique because its active ingredients –the virus strains used to develop the vaccine–change almost every year. Manufacturers therefore must produce tens of millions of doses of a new vaccine each year. Promising technologies such as cell culture and recombinant protein and DNA-based influenza vaccines are in the research and development stages and we are working with our DHHS colleagues and with manufacturers to advance their development. The most efficient vaccine production methods currently available, however, involve the use of millions of live chicken eggs to grow three different strains of influenza viruses annually. This is a complex process that spans several months during which manufacturers cultivate the appropriate strains to make the vaccine. These factors present an enormous challenge for manufacturers and create uncertainty for vaccine supply.

Every year, CBER begins working with manufacturers at the earliest stages of vaccine development, and continues to assist them throughout the production phase. We do this not only through our regulatory evaluations, but also by providing needed influenza strains and standards that can be used for efficient manufacturing. Specifically, we provide reagents to ensure that the vaccine is potent and we further evaluate the vaccine through the use and review of laboratory tests that help ensure the safety and efficacy of the vaccine. Throughout this process, CBER frequently discusses technical and manufacturing issues with manufacturers.

Influenza vaccine is highly cost-effective and beneficial to the public. Over the last decade, health care providers, CDC and others have been very successful in expanding the number of Americans who receive the vaccine. The influenza vaccine market is very fragile, however, because the increasing demand has been coupled with a decline in the number of U.S-based and U.S.-licensed manufacturers. More importantly, the market returns for producing this and many other vaccines are usually minimal, while the financial and other risks involved are great. Further, vaccine manufacturing requires careful and comprehensive controls, a complex and sometimes unpredictable manufacturing process, and highly specialized facilities that can be expensive to maintain and update. For the 2004-2005 season, only three U.S. licensed manufacturers began production of influenza virus vaccine: Chiron Corporation and Sanofi Pasteur, Inc. produced inactivated vaccine, the form currently used for most high-risk individuals, while MedImmune, Inc., manufactured FluMist, a live, attenuated (weakened and safe) influenza vaccine.

Efforts to Obtain Additional Vaccine

On October 5, 2004, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) suspended Chiron's license to manufacture influenza vaccine due to deficiencies in good manufacturing practice that led to sterility failures in filled vials of the vaccine. FDA's and MHRA's review of Chiron's investigation of the root cause of the company's sterility failures and our own review and inspections of their facility revealed problems that led FDA to conclude that the sterility, and therefore safety, of the vaccine Chiron produced for the 2004-2005 influenza season could not be assured.

The loss of Chiron's planned contribution to the U.S. influenza vaccine supply posed serious challenges

to the influenza vaccine supply for the 2004-2005 season. CBER worked urgently, aggressively and closely with CDC and other components of DHHS and the private sector to explore all viable options to secure additional doses. Working with Sanofi Pasteur and MedImmune, approximately 5 million additional doses of U.S.-licensed vaccine were secured. Sanofi Pasteur increased production to 58 million doses of Fluzone, and MedImmune scaled up to produce 3 million doses of FluMist. FluMist, which is recommended for healthy individuals 5 to 49 years of age, provided an option for those who would not receive the injectable vaccine under CDC's priority guidelines. To expand the vaccine supply to those with the greatest need, then-DHHS Secretary Tommy G. Thompson, in cooperation with the DoD, announced that the military would maximize its use of FluMist. This made an additional 200,000 doses of injectable vaccine available to DHHS for high-risk civilian populations. Through these collaborative efforts, manufacturers increased the available supply of licensed influenza vaccine for the U.S. population to 61 million doses for the 2004-2005 season, compared with approximately 83 million doses distributed in 2003-2004 and in 2002-2003, 77 million doses in 2001-2002 and 70 million doses in 2000-2001.

Because of concern that demand could still outstrip supply, we sought additional doses of vaccine that could be safely used in an emergency. Thus, in addition to enhancing the supplies of vaccine approved for use in the U.S., we rapidly identified suppliers of approximately 5 million doses of additional vaccine, licensed in other countries, which could potentially be made available under an FDA IND application. With cooperation from several companies and from other regulatory agencies (including the Paul Ehrlich Institute, Germany; Therapeutic Goods Administration, Australia; Swiss Medic, Switzerland; and Health Canada, Canada) FDA immediately sent inspectors and scientists to the manufacturing facilities of potential IND sponsors to evaluate their manufacturing processes. Coupled with these efforts, we also reviewed a large volume of manufacturing and clinical data, all within a few weeks. These efforts resulted in INDs that would have permitted the use of approximately 4 million doses from GlaxoSmithKline (GSK) and 1 million doses from Berna Biotech had they been needed. Coordinated interactions with these and other international vaccine manufacturers and regulatory agencies also provided DHHS and FDA with valuable information and strengthened relationships that helped stimulate interest by additional influenza vaccine manufacturers to pursue U.S. licensure. This is one constructive outcome of the challenges we faced this past flu season.

Plans for 2005 and Future Years

At the same time that we addressed the past year's shortage by facilitating the availability of additional influenza vaccine, we applied a dual-track strategy to help improve supply for future years:

1. Facilitate the return of Chiron as a supplier of influenza vaccine for the U.S. market; and
2. Promote expanded capacity and diversity of U.S. influenza vaccine supply.

First, the most important single factor to determine the status of the U.S. influenza vaccine supply for the 2005-2006 season was whether Chiron could correct its manufacturing problems at the Liverpool facility and supply vaccine for the U.S. market. To succeed, Chiron implemented extensive improvements needed to satisfy both FDA and the U.K.'s regulatory authority. After MHRA's suspension of Chiron's license to manufacture influenza virus vaccine at the Liverpool facility, Chiron gave MHRA and FDA permission to discuss information that could not otherwise be shared. This arrangement allowed free exchange of information as the company initiated efforts to address the problems at Liverpool. Then, on February 14, 2005, FDA signed a general information-sharing agreement with MHRA that, among other things, permitted advance communication on important issues and is not limited to Chiron's influenza vaccines. Chiron developed a comprehensive remediation plan. Both FDA and MHRA reviewed and provided extensive input on this plan and continued to provide extensive feedback to Chiron as it implemented the remediation plan. As a result of progress in the Liverpool facility, MHRA lifted its license suspension on March 2, 2005, which allowed Chiron to proceed with manufacturing plans.

Both agencies also worked together and actively communicated on inspectional activities. The FDA accompanied MHRA on work-in-progress inspections of the Chiron Liverpool facility in December 2004 and in February, May, and September 2005; MHRA accompanied FDA on its comprehensive inspection of the Liverpool facility in July 2005. In August 2005, FDA communicated to Chiron that its responses to FDA inspectional observations were generally acceptable.

On October 17, 2005, Chiron announced the release and delivery of the first Fluvirin influenza vaccine to the United States for the 2005-2006 flu season. "A tremendous amount of work by FDA, MHRA, and the firm has brought us to the point that will allow Chiron

to distribute influenza vaccine for this flu season," said Dr. Goodman. "However, as with all influenza vaccine manufacturers, Chiron's influenza vaccine must undergo safety testing and lot release evaluation before it can be released to the market." The success of Chiron's remediation plan allowed the company to market millions of doses of influenza vaccine for the 2005-2006 influenza season.

While working hard this past year to facilitate Chiron's efforts to correct its manufacturing problems, FDA also pursued a second track to improve preparedness for this and future influenza seasons and facilitate greater overall capacity and diversification of the U.S. influenza vaccine supply. It is critical to recognize, however, that demand for vaccine and other economic factors are, and will, remain the primary factors that determine:

1. Whether a manufacturer will seek and maintain licensure;
2. The strength of the manufacturing infrastructure in the United States; and
3. The amount of vaccine that manufacturers produce for the U.S. market.

These factors also apply to other vaccines and the U.S. vaccine supply infrastructure in general. Both the CDC and FDA encourage extending vaccination throughout the influenza season, including January and February. If such demand exists, manufacturers can increase total doses available by producing vaccine that becomes available during these months. Because influenza cases usually continue or peak well after the November-December time period when most individuals seek immunization, continuing vaccination is beneficial to recipients and should be encouraged.

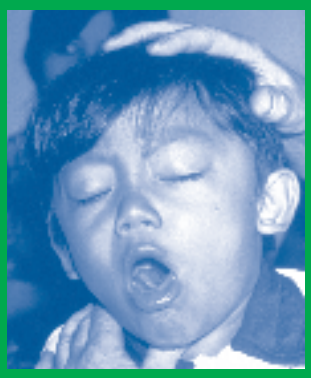
While greater production by licensed manufacturers will enable us to meet some of the influenza vaccine supply needs, recent events highlight the potential benefits of having more U.S.-licensed manufacturers. FDA has interacted constructively with several interested firms in this regard. The Agency informed manufacturers that it could consider new approaches to influenza vaccine licensing, such as accelerated approval based on surrogate markers likely to predict clinical benefit (e.g., the degree of antibody response to the vaccine), followed by post-licensure studies of clinical effectiveness against influenza illness.

For example, GSK pursued this development approach, and on August 31, 2005, FDA approved GSK's influenza vaccine, Fluarix, making it the first vaccine approved using FDA's accelerated approval process. Accelerated approval allows products that treat serious or life-threatening illnesses to be approved based on successfully achieving an endpoint that is reasonably likely to predict ultimate clinical benefit, usually one that can be studied more rapidly than showing protection against disease. In this case, the manufacturer demonstrated that adults vaccinated with Fluarix produced levels of protective antibodies in the blood that FDA believes are likely to be effective in preventing influenza. GSK will conduct further clinical studies as part of the accelerated approval process to verify the clinical benefit of the vaccine. ID Biomedical of Canada has also indicated interest in seeking accelerated approval for its influenza vaccine. It expects to complete needed studies and submit a license application in 2006 and that, if licensed, would potentially have vaccine available in time for the 2006-2007 season.

FDA Approves Vaccines to Protect Against Whooping Cough

Combination Vaccine Approved for Adolescents

On May 3, 2005, FDA approved a license application for tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap). Boostrix, the trade name of this vaccine, is indicated for active booster immunization against diphtheria, tetanus, and pertussis (whooping cough) as a single dose in individuals 10 through 18 years of age. This is the first licensed acellular pertussis-containing vaccine with an indication for adolescents.



A young boy suffers from Pertussis infection. Two vaccines were appoved in FY 2001 to help protect adolescents and adults against whooping cough.

Pertussis is a highly communicable disease of the respiratory tract that can be especially serious, possibly fatal, for infants less than 1 year old. Pertussis can cause spells of coughing and choking that make breathing difficult. The disease is generally less severe in adolescents, but it is thought that they might

transmit the disease to susceptible infants and other family members. In the last 20 years, rates of pertussis infection have been increasing among very young infants who have not received all their immunizations, as well as among adolescents and adults.

Combination Vaccine Approved for Adolescents and Adults

On June 10, 2005, FDA approved a license application for tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Tdap). This is the second Tdap vaccine to be approved this year (see above). Adacel, the trade name of this vaccine, is indicated for active booster immunization against diphtheria, tetanus, and pertussis (whooping cough) as a single dose in persons 11 through 64 years of age. This is the first licensed acellular pertussis-containing vaccine with indication for adults.

FDA Approves New Plasma-Derived Products to Treat Complications of Smallpox Vaccination

On February 18, 2005, CBER approved vaccinia immune globulin intravenous (VIGIV), the first intravenous human plasma-derived product available to treat certain rare complications of smallpox vaccination. This product is manufactured by DynPort Vaccine Company LLC. In May 2005, CBER approved a second VIGIV, manufactured by Cangene Corporation. Both of these license applications were granted priority review and approved under the accelerated approval mechanism in the regulations.[7]

The CDC classifies smallpox as a disease believed to pose the greatest threat to public health from bioterrorism, along with anthrax, botulism, and plague. Historically, up to 30% of smallpox cases are fatal. No proven treatment exists. Thus, in people who are considered at high risk for contracting smallpox, such as those who would be called upon to respond to a bioterrorist attack involving smallpox as a weapon, the benefits of the highly effective smallpox vaccine outweigh its risks.

The most common side effects from the smallpox vaccine, such as a sore arm, fever, and body rashes, are self-limiting and do not require treatment. VIGIV is indicated for rare serious vaccine complications, such as a severe infection of the skin. Those at increased risk for these complications include people with eczema or other skin conditions, and people whose immune systems are suppressed due to diseases or medications, such as steroids or cancer therapies.

FDA Approves ProQuad, a One-Dose Combination Vaccine

On September 6, 2005, FDA approved a license application for measles, mumps, rubella, and varicella (Oka/Merck) virus vaccine live. ProQuad is the trade name of this new combination vaccine, which is indicated for active immunization against measles, mumps, rubella (German measles), and varicella (chickenpox) in children 12 months to 12 years of age. ProQuad is manufactured and distributed by Merck and Co., Inc.

Potential advantages of combination vaccines include reducing multiple injections, improving timely vaccination coverage, reducing the cost of administration of separate vaccines for health care providers, and reducing costs for extra health care visits. A trivalent combination of measles, mumps, and rubella vaccine viruses has been available in the United States since the 1970s. The addition of varicella in the new combination vaccine offers several potential advantages, including the potential to improve the varicella (chickenpox) vaccination rates.

A boy with his "Official Rubella Fighter Membership Card," and button after being immunized for the disease during the rubella umbrella campaign. FDA approved a license application on September 6, 2005 for measles, mumps, rubella, and varicella.

FDA Approves New Meningitis Vaccine

On January 14, 2005, FDA approved a license application for meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine, under the trade name Menactra. Menactra is indicated for the active immunization of adolescents and adults 11 to 55 years of age for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W-135. Menactra is the first meningococcal conjugate vaccine approved in the United States. Menactra is manufactured by Aventis Pasteur, Inc. *Neisseria meningitidis* (meningococcus) is a leading cause of meningitis and septicemia in young adults

worldwide. Between 1967 and 2002, approximately 1,350 to 3,500 cases of invasive meningococcal disease occurred annually in the United States. Most human disease is caused by one of 5 serogroups (A, B, C, Y, W-135). Serogroups C and Y now account for approximately 63% of cases in the United States. Adolescents and young adults are at increased risk of meningococcal disease, particularly those entering college dormitories or military barracks. The onset and progression of meningococcal disease can be extremely rapid. Even with administration of appropriate antibiotics and intensive care, the case fatality rate remains approximately 10% overall, and up to 40% in cases of fulminant sepsis. Survivors may suffer long-term sequelae, including hearing loss, neurological disability, and limb loss.

In September 2005, FDA and CDC alerted consumers and health care providers to reports of Guillain Barre syndrome (GBS) following administration of Menactra. It is not known yet whether these cases were caused by the vaccine or are coincidental. In October 2005, FDA approved a revised package insert for this product that included this new information. The two agencies are continuing to evaluate the situation.

Project BioShield: Emergency Use Authorizations (EUAs)

On July 21, 2004, President George W. Bush signed into law Project BioShield, which provides new tools to improve medical countermeasures protecting Americans against a chemical, biological, radiological or nuclear attack. Project BioShield is a comprehensive effort overseen jointly by DHHS and DHS to develop and make available modern, effective drugs and biological products, including vaccines, to protect against attack using these weapons. The goals of Project BioShield include:

- Ensuring that resources are available to pay for "next generation" medical countermeasures. Project BioShield will allow the government to buy improved/new vaccines or drugs. The FY 2004 appropriation included $5.6 billion over 10 years for the purchase of next-generation countermeasures against anthrax and smallpox, as well as other agents;
- Expediting the conduct of NIH research and development of medical countermeasures based on the most promising recent scientific discoveries; and
- Giving FDA the ability to make promising treatments quickly available in emergency situations. This new authority will enable access to the best available treatments in the event of a crisis.

Project BioShield has increased the pace of product development, and CBER has been proactively helping other agencies and manufacturers to develop these products; evaluating product safety, effectiveness, and manufacturing quality; and, helping to expedite product availability as needed. With regard to the emergency use authorization (EUA) provided for in Project Bioshield, CBER worked with other components in the FDA to develop the Draft Guidance: Emergency Use Authorization of Medical Products, which was issued for comment in July 2005 (http://www.fda.gov/cber/gdlns/emeruse.htm).

The Center's role in evaluating products for emergency use, particularly when they are not yet licensed, is critical. Not only is it vital in meeting potential threats of terrorism, but also in assuring, to the extent possible, that all available data are objectively reviewed in evaluating products for potential emergency use. It is also critical to ensure that product information is completely and clearly communicated to the public. CBER reviewed the scientific data in support of DoD's request for emergency use authorization (EUA) of BioThrax, the licensed anthrax vaccine, for persons in the military at high risk of exposure to a possible attack with anthrax. The Commissioner granted this, FDA's first EUA, on January 27, 2005, and extended the EUA in July 2005, at DoD's request and after another review by CBER. At CDC's and DoD's request, CBER has reviewed data to support the use of investigational smallpox vaccines and the licensed anthrax vaccine for an unlicensed use in advance of an emergency, so-called "pre-EUAs." In addition, CBER has implemented a tracking system and standard operating procedure for administrative handling of EUAs and pre-EUAs.

Protecting America from Terrorism

The Agency, including CBER, has adopted five broad strategies for countering terrorism:

- Awareness: Increasing awareness through collecting, analyzing, and sharing information and knowledge.
- Prevention: Identifying specific threats or attacks that involve biological, chemical, radiological, or nuclear threats.
- Preparedness: Developing and making available medical countermeasures such as drugs, devices, and vaccines.
- Response: Ensuring rapid and coordinated response to any terrorist attack.
- Recovery: Ensuring rapid and coordinated treatment for any illness that may result from a terrorist attack.

CBER is responsible for helping to ensure that safe and effective biological products are available for diagnosing, treating, and preventing illness due to terrorist agents. These products include vaccines, blood and blood derivatives, gene therapies, and cells and tissues for transplantation.

These products are carefully reviewed, and risk-to-benefit issues carefully considered throughout their development, manufacturing, and clinical testing. Staff guide the products through the regulatory process, including manufacturing, pre-clinical testing, clinical trials, and the licensing and approval processes. Experts in diverse areas help expedite the development, evaluation, and approval process. Time is often of the essence and the scientific and product issues are extremely challenging. Early involvement by scientific, statistical/epidemiological, and clinical review staff is crucial to the success of the expedited development and review processes.

As part of national policy, a high priority is placed on Category A agents, a designation the CDC gives to the greatest threats to public health. Category A agents include the organisms that cause anthrax, plague, smallpox, tularemia and viral hemorrhagic fevers, as well as botulinum toxin. Emergency response proficiency is also being addressed through reassessing and strengthening capabilities and the development of continuity of operations plans. In addition, CBER has been proactive in identifying the gaps that exist related to needed medical countermeasures against biological agents that could be used in an attack.

Anthrax

Anthrax is an infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. There are 3 forms of anthrax infection: 1) cutaneous, 2) gastrointestinal, and 3) inhalational, which is associated with the highest death rates.

There is currently one anthrax vaccine, BioThrax, manufactured by Bioport Corporation, licensed in the United States. This vaccine is indicated for pre-exposure prophylaxis against *Bacillus anthracis* (the causative agent of anthrax) in individuals between 18 and 65 years of age who are at risk of exposure to anthrax. In January and April 2005, CBER approved supplements to the BLA for BioThrax to increase the manufacturing capacity and extend the dating period of the product to 36 months.

FDA also issued a proposed rule and order regarding the safety and efficacy of certain bacterial vaccines and toxoids, including the licensed anthrax vaccine, which was published December 29, 2004. After reviewing the comments submitted to the docket, CBER, together with other FDA components, issued a final rule and order regarding the safety and efficacy of certain licensed biological products and a final order regarding the safety and efficacy of anthrax vaccine on December 15, 2005.

CBER is part of an interagency working group, with NIH, CDC, DoD, and DHHS, focused on encouraging the development of new recombinant anthrax vaccines intended to prevent anthrax both before and after exposure. Such vaccines are being developed under IND, which presents many challenges, especially in terms of developing reproducible animal models for demonstrating efficacy. The genetic makeup of anthrax is being studied to help improve vaccines and treatments.[8-9]

DHHS awarded the first contract under Project Bioshield to VaxGen for its recombinant protective antigen (rPA) anthrax vaccine. CBER has devoted extensive resources to assist and guide this and other manufacturers through the regulatory process in the development of their rPA anthrax vaccines and has provided extensive technical input to the Office of Research and Development Coordination (ORDC) in the Office of the Assistant Secretary for Public Health and Emergency Preparedness (OASPHEP), DHHS, in this regard. New immune-based therapies for treating anthrax are also under development. For example, anthrax immune globulin is under evaluation as a potential treatment of anthrax disease. CBER has been working with CDER to develop a draft guidance that addresses the development and licensure of immune-based therapies to treat anthrax disease. CBER has also provided technical input to HHS, which is considering which anthrax therapeutics to potentially add to the Strategic National Stockpile.

Smallpox

Smallpox, caused by the variola virus, is highly contagious and can be spread by close contact with an individual who has smallpox symptoms - high fever, fatigue, headaches, backaches, vomiting, rash, and pus-filled blisters. There is no proven treatment. The last confirmed case of smallpox in the United States was in 1949, and the last naturally occurring case in the world was recorded in Somalia in 1977. The death rate in the past was about 30%, and death rates can be higher for infants and young children.

Smallpox can be prevented through vaccination. Dryvax (smallpox vaccine, dried, calf lymph type), made by Wyeth Laboratories, is the only smallpox vaccine

currently licensed and is no longer being manufactured. Smallpox vaccines that are related to the same vaccine strain used in Dryvax but grown in cell culture are being developed. In addition, CBER is facilitating efforts underway to develop potentially safer smallpox vaccines (e.g., modified vaccinia Ankara).[10-11]

Blood Supply

Any time there are large emergencies or outbreaks of diseases, the blood supply is threatened. In the case of mass vaccinations, those who receive vaccinations containing live viruses cannot be blood donors for a period of time because of the potential to transmit the vaccine virus. The Center has issued guidances on reducing the risk of transmitting diseases through blood donated by infected individuals, either by vaccination or by exposure to a bioterrorist agent. Recommendations have also been made for national emergency planning to ensure that vaccination campaigns consider blood supply. Efforts are also underway to produce diagnostic assays to detect bioterrorist agents in blood donations.[12]

According to the American Association of Blood Banks (AABB), a disaster would include: an act of terrorism that requires a much larger amount of blood than usual; one that temporarily restricts blood collection, testing, and distribution; or one that creates a sudden influx of donors requiring accelerated drawing of blood. CBER works with multiple partners to help assure that blood donations would remain safe and plentiful in times of disaster.

Other Counterterrorism Activities

Other major counterterrorism activities during FY 2005 include:

- CBER has led the effort to write new labeling regulations for medical products purchased for the strategic national stockpile;
- CBER has provided extensive support to the Office of Research and Development Coordination (ORDC) in the Office of the Assistant Secretary for Public Health and Emergency Preparedness (OASPHEP), DHHS. The Center has reviewed and provided technical input on multiple requests for proposals (RFPs) for acquisition of additional countermeasures for the SNS (anthrax therapeutics, new smallpox vaccines, botulinum antitoxin, neutropenia), provided information on types of data needed to consider use of unapproved countermeasures under an EUA (modified vaccinia ankara smallpox vaccine, anthrax immunoglobulin, botulinum antitoxin), and participated in the Project Coordination Team (PCT) efforts for the first contract awarded under Project BioShield for recombinant PA (rPA) anthrax vaccine;
- CBER has held numerous pre-IND/technical meetings with potential manufacturers of medical countermeasures to assist in their development and the submission of an IND; and
- CBER researchers are studying or developing: smallpox vaccine safety (neurovirulence); improved immunologic assays for anthrax vaccines; the protective isotypes of vaccinia immune globulin; correlates of immunity for tularemia; the cellular trafficking of botulinum toxin; and stimulation of innate immunity against various agents.[13-20]

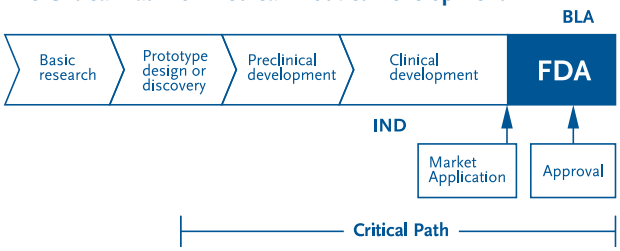
Critical Path Initiative: Better Methods to Predict Medical Product Safety and Efficacy

FDA's Critical Path Initiative emphasizes the importance of product developmental science for better and more efficient evaluation of medical products. As the nation's regulatory experts, FDA staff play a crucial role in modernizing and developing the evaluative pathways for products through their unique dual expertise in medical product development and scientific disciplines, their special view of the problems and solutions that impact across whole product categories, and their ability to prioritize and actively pursue resolutions to these challenges that are often underserved or overlooked in other scientific venues. FDA's role in active facilitation of medical product development will resolve the significant challenge of moving innovative biomedical discoveries to real medical products to save lives.

Critical Path science for complex biological products includes development and evaluation of important scientific tools. These tools include methods to measure the quality, identity and purity of complex vaccines, blood products and gene/tissue/cell therapies, as well as the necessary standards and references to accompany those methods. Another challenge includes the ability to apply qualified biomarkers indicative of product efficacy

to improve efficiency and cost-effectiveness of clinical trials, and to evaluate improved pre-clinical tests, i.e., ways of predicting product efficacy and safety prior to administration to humans.

The Critical Path for Medical Product Development



During FY 2005, many innovative achievements were realized through collaborative science. Post-marketing safety summaries have been completed and published on the most recent hepatitis vaccines, and post-marketing surveillance preparations begun for new influenza vaccines. Important activities for standardization of reagents for biological products continued, including for pandemic and annual influenza vaccines, blood products and allergenic products. Formal risk assessments are under development to assess the risk of variant Creutzfeldt-Jakob disease (vCJD) to blood derivatives, such as clotting factors. Methods to inactivate agents of transmissible spongiform encephalopathies (TSE) from medical products and methods to advance vaccine and blood product quality testing through mass spectroscopy and nuclear magnetic resonance are under evaluation. Blood safety is further enhanced by improved blood donor testing kits for the detection of variable HIV strains, West Nile virus, and hepatitis viruses.

Additional science evaluation activities included:

- Continuing evaluation of vaccine safety after licensure by identifying and studying adverse events in vaccinated children and adults, e.g., rotavirus and intestinal disease, pneumococcal vaccine and allergic responses, and influenza vaccine/meningitis vaccine and neurological diseases;
- Developing and evaluating tests to better predict the protective response to biodefense vaccines, e.g., smallpox, botulism, anthrax;
- Evaluation and qualification of biomarkers predictive of medical product safety to streamline clinical trials and support personalized medicine, e.g., biomarkers of cancer or autoimmune risk following cellular therapies and of enhanced disease following tuberculosis vaccination;
- Development and evaluation of formal risk assessments and methods to develop risk reduction strategies for products under investigation, e.g., cell and gene therapies;
- Evaluating new methods for enhancing vaccine efficacy, e.g., DNA vaccination for influenza to protect broadly across many strains, new adjuvants to boost vaccine responses;
- Modernizing and streamlining rapid tests of product quality, e.g., improved methods for vaccine quality testing, including genomics microarray to test for purity; and,
- Developing and evaluating scientific tools using 21st century technology to better characterize complex biological products to improve product quality and consistency, e.g., nuclear magnetic resonance (NMR) for better characterization of carbohydrate components of bacterial vaccines and to detect vaccine contamination and adulteration, mass spectroscopy for characterization of anthrax vaccine, and new methods that yield more consistent meningitis vaccine products.

CBER science leads the evaluation and management of a risk-based approach to current regulatory pathways and resolves anticipated regulatory challenges before and after they arise. CBER's unique expertise in complex biological product development and scientific disciplines allows application of special scientific knowledge and tools to facilitate determination of a biologic product's safety, efficacy and consistency of manufacturing.

User Fee Programs

PDUFA

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA). This was reauthorized by the Food and Drug Administration Modernization Act of 1997, and again by the Public Health Security and Bioterrorism Preparedness and Response Act of 2004. The PDUFA authorizes FDA to collect fees from companies that produce certain human drug and biological products. When a company seeks FDA approval for a new drug or biologic prior to marketing, the company must submit an application along with a fee to support the review process. In addition, companies pay annual fees for each manufacturing establishment and for each prescription drug product marketed. In this program, industry provides added resources needed to meet review performance goals, which emphasize timeliness while maintaining safety and efficacy of FDA-approved products.

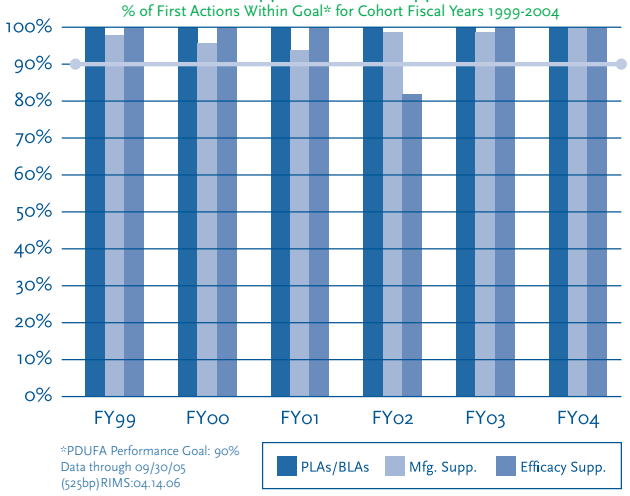
PDUFA has provided FDA with needed resources for the review of human drug and biologic applications. Fees collected have been used to help reduce the time required for evaluating human drug applications and to support review quality. FDA has submitted annual performance and financial reports to Congress on progress in streamlining the drug review process and use of PDUFA fees. The user fee legislation, amended and extended through September 30, 2007, is now referred to as PDUFA III.

In April, 2005, guidance for review staff and industry entitled "Good Review Management Principles and Practices (GRMPs) for PDUFA Products" was issued. The guidance supports the FDA's primary public health mission for human drug and biologic products, helps the FDA continue to define processes that fulfill the Agency's PDUFA mandates, promotes efficient use of the FDA's resources, and defines ways in which both FDA review staff and applicants can make the review process more efficient. This guidance is expected to lead to greater consistency and efficiency of the review process within individual review divisions, across review divisions, and between CDER and CBER. The GRMPs in this guidance are based on the collective experience of these two centers with review of applications for PDUFA products and are intended to promote the practice of good review management based on sound fundamental values and principles. Representatives from CBER, CDER, and the Commissioner's office are currently preparing for negotiations with industry on PDUFA IV.

CBER User Fee Review Performance

License Application and Supplements

% of First Actions Within Goal* for Cohort Fiscal Years 1999-2004



MDUFMA

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) is providing needed funds to FDA for "the review of devices and the assurance of device safety and effectiveness so that statutorily mandated deadlines may be met." Congressional appropriations for FDA's medical device program had been reduced in recent years, and there were indications that review performance had begun to decline. The user fees provided by MDUFMA, as well as the additional appropriations approved with the new law, have helped reverse that trend and are providing the following continuing benefits:

- Safe and effective devices used to diagnose and treat disease are reaching the public more rapidly;
- Manufacturers are receiving timely, high-quality application reviews; and,
- Devices marketed in the United States continue to meet high standards for safety and effectiveness.

CBER 510k Average Review Time

Receipt to Final Action

FY 2002-FY2006

	FY02	FY03	FY04	FY05	FY06
CBER Review Time (days)	114.0	57.1	64.6	68.6	40.6
Average Number of Cycles	1.7	1.3	1.4	1.5	1.1

Includes SEs/NSEs/WDs

Data through March 31, 2006

In the last three years, CBER has sought input from both inside and outside the Agency to strengthen the quality, efficiency, and timeliness of its device review process. The resulting increased effectiveness of device review in CBER is illustrated by the fact that CBER has met FY 2005 MDUFMA goals for all types of application submissions in 2004. In many cases, these approvals relate directly to innovations that enhance the safety and efficacy of blood and tissue products. Timely approvals included products for which we received modular pre-market approval applications (PMAs).

In addition, CBER interaction with government partners and industry has facilitated the recent approval of rapid tests for HIV and of tests to monitor HIV drug resistance, examples of successful regulation under the framework established by MDUFMA.

The Center aims to apply regulation in a risk-based manner. Certain areas in CBER's oversight, including blood screening tests, raise unique concerns. CBER seeks to address these in a balanced, transparent, and least burdensome manner and welcomes public and industry input.

In the spirit of the least burdensome approach to regulating devices, on November 17, 2004, CBER/CDRH issued guidance to industry that provided FDA's recommendations on the timeliest and most effective way to resolve disputes concerning FDA actions that affect payment or a refund of a user fee assessed under MDUFMA. Other guidances were also issued during FY 2005. A guidance was issued to Industry, FDA staff, and FDA-accredited third parties on requests for inspection by an accredited person under the inspection by accredited-persons program, authorized by Section 201 of the Act.

CBER has met or exceeded the MDUFMA review performance goals, most of which became effective in FY 2005. For the first two years of MDUFMA, only 2 of the performance goals were in place. In FY 2005, 20 MDUFMA goals are in place, and the Agency is collecting data on its performance against these goals. The Agency MDUFMA performance and finance reports can be accessed at www.fda.gov/oc/mdufma.

Representatives from CBER, CDRH, and the Commissioner's office are currently preparing for negotiations with industry on MDUFMA II.

Cellular and Gene Therapies: Facilitate Availability and Development of Safe and Effective New Technologies

Genomics and Proteomics

As hundreds and thousands of endpoints may be analyzed simultaneously, genomics and proteomics offer novel approaches to understanding biological processes. Not only are these technologies being incorporated into the routine of academic laboratories, but they are also becoming a tool for biotechnology, product characterization, and clinical research conducted by both academia and industry. There is a consensus that it will not be long before the results of genomic and proteomic studies will appear in INDs and BLAs/New Drug Applications (NDAs) submitted to FDA. To facilitate development and availability of safe and effective technologies, the Office of Cellular, Tissue, and Gene Therapies (OCTGT) staff is engaged in the research and development of standards, performing critical path research to characterize products including cellular and gene therapy products and developing guidance documents in the area of genomics and proteomics technologies.[21-22] The OCTGT staff is also engaged in developing expertise within the FDA/CBER by providing a hands-on training program for regulatory scientists and research reviewers. More than 50 regulatory scientists/research reviewers have been trained through this program.

Scientists within the OCTGT helped develop the FDA guidance for industry, "Pharmacogenomic Data Submissions," which was released in March 2005. These scientists are also involved in the FDA's Interdisciplinary Pharmacogenomics Review Group (IPRG), which evaluates voluntary genomics data that regulated industry submits to FDA.

Tissue Engineering

In support of the critical path element entitled, "Tools for Assessing Safety, Demonstrating Medical Utility, and Characterization of Manufacturing," OCTGT, together with CDRH is developing a partnership with other federal agencies with the intent to advance tissue engineering science and to facilitate the development of safe and effective tissue-engineered products.

The OCTGT has met with product manufacturers currently developing these innovative products and has a unique perspective pertaining to the issues associated with the early phases of developing tissue-engineered products. The need to provide a clear strategy that defines the types of studies and data essential for supporting regulatory submissions has been consistently noted. For example, OCTGT has identified a need for criteria suitable for the characterization of final manufactured cell-scaffold tissue-engineered products. Key issues being considered include: 1) What questions should be asked and addressed by testing, and at what stage of product assembly? and 2) What testing methods are available and what methods need to be developed?

Gene Therapy Clinical Trials: Observing Patients for Delayed Adverse Events

In August 2005, CBER issued draft guidance for industry on observing participants in gene therapy clinical trials for delayed adverse events. This draft guidance provided sponsors of gene therapy studies recommendations regarding the design of studies to include the collection of data on delayed adverse events in participants who have been exposed to gene therapy products. It provided recommendations on: 1) methods to assess the risk of gene therapy-related delayed adverse events following exposure to gene therapy products; 2) determining the likelihood that long-term follow-up observations on study participants will provide scientifically meaningful information; and 3) the duration and design of long-term follow-up observations. The guidance discussed the importance of long-term follow-up observations when the risks to human subjects presented by a gene therapy clinical trial continue into the long term, in order to mitigate those risks.

This draft guidance also set forth criteria that CBER developed to assess potential delayed risks of gene therapy. To assess the risk related to specific products, CBER recommended that industry use available preclinical and clinical evidence. To assess the risks of delayed adverse events, industry may use current information about their product and similar products based on studies that they and others have performed. As more data accumulate, it is important to reassess the risk to participants and, if appropriate, revise protocols with regard to long-term follow-up observations.

We consider the assessment of risks to be a continuous process. New information may support the need for long-term follow-up observations or the revision of an

existing study. For example, if recently reported evidence suggests a newly identified risk associated with the specific product or similar products, long-term follow-up observations may be necessary to mitigate long-term risks to subjects receiving these vectors. Similarly, if sufficient data accumulate to suggest that the product is not associated with delayed risks, it may be appropriate to reduce or eliminate provisions for long-term follow-up observations.

Cellular and Gene Therapy: Outreach and Partnerships

Cellular and gene therapies are novel and rapidly evolving product classes that require early scientific and regulatory interaction with investigators, industry, patient advocates, and the public. CBER continues to place a high priority on activities that promote both the development of these novel products and the reduction of time to market, while maintaining the standards of safety and effectiveness. Early and continuing interactions with stakeholders and the public have proven to be an effective means of communicating, addressing issues regarding potential risks and benefits, and avoiding unnecessary regulatory burdens. Following are some examples of these interactions during the past fiscal year.

In October 2004, at CBER's workshop entitled "From Concept to Consumer: Center for Biologics Evaluation and Research, Working with Stakeholders on Scientific Opportunities for Facilitating the Development of Vaccines, Blood and Blood Products, and Cellular, Tissue, and Gene Therapies," CBER held a breakout session on cellular and gene therapies. At that session, representatives of academia, industry, other government agencies and patient advocacy groups discussed approaches to facilitate development of cellular and gene therapy products. Topics included methods and standards development, product characterization research, biomarker and preclinical research, clinical endpoints, and conduct of clinical trials and the regulatory science interface. A summary of this session was published in the *Journal of Molecular Therapy* (12, no.1 July 2005, pg.5-8).[23]

On November 5, 2004 and June 24, 2005 CBER staff attended the Cell Therapy/FDA Liaison Meetings the purpose of which was to discuss important issues of mutual interest. Topics discussed at the two cited meetings included combination products, establishment of a definition for homologous use, and general facilities requirements for manufacturing of cell and tissue products.

In March of 2005, CBER staff held a Cellular, Tissues and Gene Therapies Advisory Committee meeting to discuss issues related to cellular therapies for the repair and regeneration of joint surfaces. The issues included product characterization and testing, preclinical animal models, and clinical trial design. The meeting also included an update on retroviral vector-mediated insertional mutagenesis.

In April 2005, CBER staff attended and presented at an ASGT meeting entitled "Challenges in Advancing the Field of Gene Therapy: A Critical Review of the Science, Medicine and Regulation-Stakeholders Meeting." The objectives of the meeting were to bring members of the gene therapy community together to critically review the issues and consider ways to move the field forward and specifically facilitate the initiation and successful conduct of gene therapy clinical trials.

In May 2005, CBER staff attended and co-chaired the International Conference on Harmonization (ICH) Gene Therapy Discussion Group (GTDG) meeting held in Brussels, Belgium. At this meeting the group discussed issues related to the potential for inadvertent germline transmission of gene therapy products and the safety and benefit of using oncolytic viruses for use in oncology clinical trials. The GTDG also finalized the agenda for a Workshop on Oncolytic Viruses to be held in November 2005 at the next ICH meeting in Chicago and also received the steering committee's approval to draft an "ICH Considerations" document on Minimization of the Risk of Inadvertent Germline Transmission of Gene Therapy Vectors.

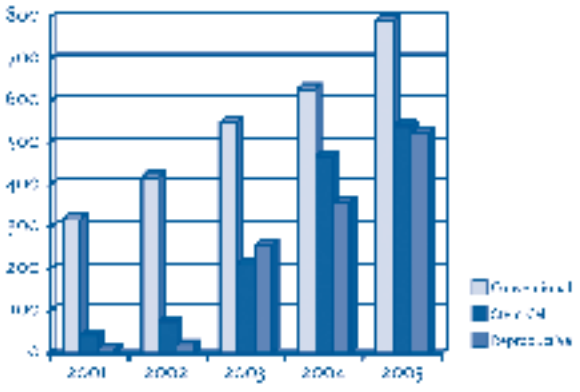
On September 22 and 23, 2005, CBER staff attended and presented at the Korean FDA International Symposium and gave the lecture entitled, "Current Issues on Xenotransplanation." CBER staff also presented a talk entitled, "Overview of Xenotransplanation Regulation in the U.S.," at the follow-up seminar: Colloquium on the Regulatory Aspects on Xenotransplanation. This two-day meeting allowed the U.S. FDA and the Korea Food and Drug Administration (KFDA) to participate in ongoing discussions on the safety concerns surrounding clinical trials using xenotransplanation products.

ENHANCING PATIENT AND CONSUMER PROTECTION AND EMPOWERING THEM WITH BETTER INFORMATION ABOUT REGULATED PRODUCTS

New Rules for "Good Tissue Practice"

The final rule on current good tissue practice (GTP), the last of three rules to be issued as part of FDA's strategic approach to the regulation of human cells, tissues, and cellular and tissue-based products, was published in the *Federal Register* on November 25, 2004. This new rule, entitled "Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement," requires manufacturers to recover, process, store, label, package, and distribute human cells, tissues, and cellular and tissue-based products (HCT/Ps), and screen and test cell and tissue donors, in a way that prevents the introduction, transmission, or spread of communicable diseases. This final rule completes FDA's efforts to establish a new, comprehensive, and risk-based approach to this promising and innovative field of medicine. The regulations apply to a broad range of products including musculoskeletal tissue, corneas, human heart valves, dura mater (lining of the brain) and cellular therapies. The new approach became effective on May 25, 2005.

Establishments Registered



Two other related rules to implement the proposed regulatory approach to HCT/Ps were previously finalized. The first final rule, "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing," was issued on January 19, 2001. It became effective on April 4, 2001, and requires HCT/P establishments to register with the FDA and list their products.

The other final rule, "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products," was issued on May 25, 2004, and focuses on donor screening and testing measures to prevent the unwitting use of contaminated tissues with potential to transmit infectious diseases. It became effective on May 25, 2005, and applies to all HCT/Ps, including reproductive cells and tissues recovered on or after that date. Additional information about FDA's efforts to make the nation's tissue supply even safer is available online at www.fda.gov/cber/tissue/docs.htm.

Response to Transfusion-Transmitted Emerging Infectious Diseases and Other Public Health Concerns

West Nile Virus

The United States has experienced a West Nile virus (WNV) epidemic each summer for the past several years. In 2002, FDA and CDC, working together, identified transmission of WNV by blood transfusion. In response, FDA encouraged the development of investigational WNV nucleic acid tests (NAT) as screening tests and facilitated the widespread study of these investigational tests by blood establishments. Beginning in July 2003, investigational WNV NAT was available throughout the country to screen the blood supply in a minipool (6-16 sample) format, and more than 95% of the blood supply was tested. In 2003 and 2004, blood screening for WNV detected more than 1,000 viremic donors and prevented their donations from entering the blood supply. Rare cases of transfusion-transmitted WNV continued to be reported in 2003 and 2004, however, from transfused units that contained extremely low levels of virus not detected by minipool NAT. In 2005, WNV continued to spread across the lower 48 continental states with about 2,300 cases of WNV illness and 66 deaths reported in the general population. Although the highest activity level occurred in California, WNV

activity continued to occur throughout the United States at a greater frequency than in 2004. During the epidemic of 2005, blood screening for WNV detected more than 350 viremic donors and prevented their donations from entering the blood supply up until October 2005. No cases of transfusion-transmitted WNV were reported in 2005. To further enhance blood safety, voluntary individual investigational donor testing was implemented during periods of high disease activity in high-incidence areas.

Between September 2002 and October 2005, investigation of 30 recognized cases of WNV transmitted by blood transfusion documented to date indicated the infectious donors' viremia can be of low titer and that all resulted from IgM antibody negative donations. Conversely, transfused viremic donations that were recognized only after retrospective testing did not transmit WNV infection if IgM antibody was present. Laboratory investigations at CBER, however, demonstrated WNV infectivity in cell culture of blood donor samples that were IgG and/or IgM positive, suggesting the possibility of transmission by antibody-positive NAT negative donations.[24]

There was a report of WNV transmission from an organ donor to 3 of 4 organ recipients in New York and Pennsylvania in September 2005. A sample from this donor tested positive for WNV IgG and IgM, but negative by individual donor test NAT. One possibility is that WNV remains in organs after it is cleared from the blood.

FDA continues to work with CDC, the NIH and other PHS partners, as well as with an AABB WNV task force, to monitor the WNV epidemic. As described below, FDA continues to update its guidance documents as the science evolves.

Bacterial Contamination of Platelets

Bacterial contamination, especially of platelets, remains among the top three causes of transfusion-related fatality in the United States. To address this problem, FDA has encouraged the development of bacterial detection devices that can be used to test platelets before their release. To date, FDA has cleared three devices for quality control monitoring of the platelet collection process (bioMerieux BacT/Alert, Pall eBDS, Hemosystems Scansystem). Sensitivity for detecting bacteria is in the range of 10-100 colony forming units (CFU)/ml. Other non-approved and non-validated methods such as swirling and glucose and pH dipsticks are being used to meet a voluntary AABB standard for bacterial detection that became effective in March 2004. In February 2005, the FDA approved Gambro BCT single-donor platelets for 7-day storage. The FDA approved the extension of platelet shelf life from 5 days to 7 days when the Gambro BCT collection bag is used along with the bioMerieux BacT/Alert Microbial Detection System using both aerobic and anaerobic culture bottles. FDA is also encouraging studies to validate pre-storage pooling of platelets derived from platelet-rich plasma.

Immune Globulin Availability

Starting in January 2005, the Department of Health and Human Services (DHHS), FDA and the Centers for Medicaid and Medicare Services (CMS) began receiving an increased number of reports that health care providers were having difficulty obtaining immune globulin intravenous (IGIV) for some patients. FDA worked cooperatively with DHHS and the Plasma Protein Therapeutics Association (PPTA) to monitor the IGIV supply and facilitate its availability. From approximately August 2003 to July 2005, the average monthly distribution of IGIV had remained relatively flat, while demand has historically increased by 7%-10% per year. However, from August 2005 to December 2005 the average monthly IGIV distribution increased by about 16% compared to the previous 12 months. While there does not appear to be a severe product shortage, there have been reports of difficulties obtaining the same product in the same treatment center that patients customarily use. Treatment locations have shifted from physicians' offices to hospital settings. The disruptions in treatment locations reportedly were due to changes in reimbursement practices.

At the July 2005 meeting, the Blood Products Advisory Committee (BPAC) discussed the decision by Massachusetts Public Health Biological Laboratories (MPHBL) to stop manufacturing varicella-zoster immune globulin (VZIG.) MPHBL is the sole manufacturer of VZIG, which is used to prevent severe complications of varicella-zoster infection. FDA sought the Committee's advice on options for efficacy determination for new BLA applications for VZIG because of concerns about a potential upcoming shortage of this product. The FDA will facilitate efforts of manufacturers to develop new

VZIG products and to make product available under investigational mechanisms. Currently, an investigational VZIG is available under an expanded access protocol, for use in patients who are susceptible to severe varicella-zoster virus infection.

CBER Response to Emergencies: Blood Supply & PHS Staff Support

As part of the National Response Plan, FDA cooperates with DHHS and other PHS partners and with the U.S. Department of Homeland Security (DHS) in responding to emergency situations. In January 2002, four months after the terrorist events of September 11, 2001, the AABB established the Inter-organizational Task Force on Domestic Disasters and Acts of Terrorism (Task Force). The AABB Task Force was formed "to make certain that blood collection efforts resulting from domestic disasters and acts of terrorism run smoothly and are managed properly, with the public receiving clear and consistent messages regarding the status of America's blood supply." The Task Force includes representatives from various blood services and associations, governmental agencies including the FDA, CDC, NIH, Department of Defense (DoD), and device manufacturers, who work together to ensure that facilities maintain safe and adequate inventories at all times in preparation for disasters, and have a mechanism in place to assess the need for collections and/or transportation of blood should a disaster occur.

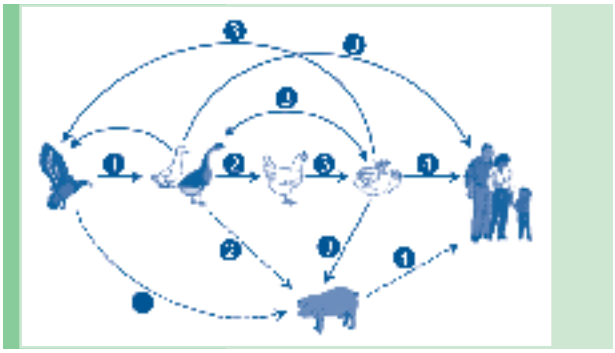
Staff members from CBER's Division of Blood Applications (DBA) are Level 1 members of the AABB Inter-organizational Task Force. The Task Force is activated in the event of a disaster, to determine the medical need for blood, facilitate transportation, and communicate a common message to the public. When necessary, these activities are also coordinated with DHHS (also a Level 1 member). The Office of Blood Research and Review (OBRR) in CBER also participates in any Task Force subgroups as needed to examine, for example, donor deferral issues.

During 2005, the United States experienced a series of hurricanes that dramatically impacted the Gulf Coast and Florida. PHS staff were mobilized and deployed to respond to the public health emergency created by the very significant displacement of persons. CBER staff who deployed for hurricane relief efforts dedicated a large amount of time providing needed medical care. In addition, the OBRR staff met as part of the AABB Task Force to ensure that blood was available to affected areas. Where needed, advice or approval of variance requests were made to ensure that blood was available to hospitals during the emergency. OBRR staff communicated the outcomes of the AABB Task Force meeting to CBER leadership, who kept the FDA's Office of Crisis Management informed.

Pandemic Influenza Preparedness

The Department of Health and Human Services is helping to transform the influenza marketplace and reinvigorate the influenza vaccine infrastructure by investing in promising new technologies, securing additional vaccines and medicines, and preparing stronger response plans and capacity. Furthermore, the lessons we have learned and insights gained from recent experiences with influenza vaccine will be critical factors in preparing for an influenza pandemic. Given the eventual likelihood of an influenza pandemic and the recent outbreaks of avian influenza in many countries, this is an issue of highest concern for FDA and others in the public health community.

More widespread vaccination during periods between pandemics not only has direct health benefits but also will increase vaccine production capacity and help America and the global community better prepare for an influenza pandemic.



As part of DHHS efforts to support pandemic preparedness, the National Institute of Allergy and Infectious Diseases (NIAID) contracted for the production of pilot lots of potential pandemic vaccines from two licensed U.S. manufacturers. DHHS contracted for the production of 2 million doses of vaccine against H5N1 avian influenza, the influenza subtype of current concern. The NIAID recently initiated critical clinical studies of the first H5N1 vaccine under INDs that FDA oversees, and both agencies will be evaluating the results. While much work remains, these steps to produce and evaluate pandemic influenza vaccines are a critical component of our preparedness efforts. They will inform us about the needed dosing and scheduling of pandemic vaccine and pave the way for evaluation, potential licensure, and broader use of a vaccine against avian influenza if needed.

In addition, NIH and FDA support studies to develop vaccine strategies that could lead to longer-lived

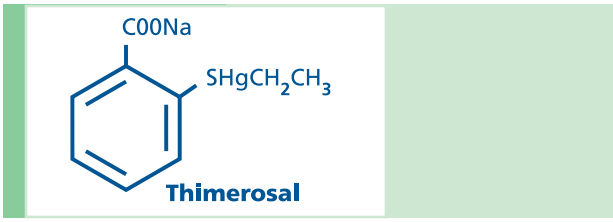
immunity and the production of an immune response that could potentially allow one year's vaccine to provide immunity over multiple flu seasons. The FDA is actively engaged with sponsors and manufacturers interested in developing new technologies for influenza vaccine manufacture, including cell-culture based and recombinant vaccines.[25-26]The Agency has extensive experience in overseeing the development and licensure of cell-culture based and recombinant vaccines including those for prevention of other infectious diseases, such as chicken pox, polio, rubella, and hepatitis A and B. The FDA's goal is to support a process to produce pandemic influenza vaccine in the shortest amount of time possible and protect the largest number of people, using a vaccine that is safe, effective, and easy to deliver. The full details of the draft Pandemic Influenza Preparedness and Response Plan are located on the DHHS Web site at http://www.dhhs.gov/nvpo/pandemicplan/annex5.pdf. Through these efforts, and with enhanced global surveillance by CDC and its partners, we have a unique opportunity to intervene effectively and potentially blunt a global pandemic.

Although we may never completely prevent influenza outbreaks, we can greatly decrease our vulnerability and provide protection against influenza with a robust vaccine supply supplemented by effective anti-virals. The FDA recognizes the need to continue working with multiple partners, including manufacturers, to increase supply and to support progress toward more modern, dependable methods of production. The steps we have discussed will not only help protect Americans from influenza every year but will help prepare us for future influenza seasons or a possible influenza pandemic.

Thimerosal in Vaccines

The widespread use of pediatric vaccines has contributed to a significant reduction of many childhood diseases such as diphtheria, polio, measles, and whooping cough. It is now rare for American children to experience the devastating effects of these illnesses, and infant deaths due to these diseases have essentially disappeared in countries such as the United States, which have high vaccination coverage rates. As a recent example, prior to the introduction of a vaccine in 1985, an estimated 20,000 cases of invasive *Haemophilus influenzae* type b (Hib) disease, primarily meningitis, occurred annually in the United States. Now, because of widespread vaccination, the number of cases of invasive Hib disease has decreased by more than 98%. In the United States, Hib infection was the leading cause of acquired mental retardation.

Although vaccines have contributed greatly to the health and wellbeing of our children, we must nonetheless remain vigilant for any potential vaccine-related safety concerns. One such safety concern involves the use of thimerosal as a preservative in routinely recommended licensed pediatric vaccines. Thimerosal, a mercury-based compound containing ethylmercury, is used as a preservative in some multi-dose vials of vaccine, and has a long record of safe and effective use in preventing bacterial and fungal contamination of vaccines. In response to Section 413 of the FDA Modernization Act (FDAMA) of 1997, CBER conducted a review of the use of thimerosal in childhood vaccines. This review led to the realization that some children, during their first 6 months of life, might receive amounts of ethylmercury from the preservative, thimerosal, in excess of the U.S. Environmental Protection Agency's (EPA) guidelines for methylmercury, but not in excess of the FDA or World Health Organization (WHO) guidelines. Although there were no known risks from these levels of thimerosal in vaccines, the Public Health Service, along with the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) concluded that it was prudent to reduce childhood exposure to mercury from all sources, including vaccines, as feasible.



Consistent with this goal, CBER has encouraged and worked with manufacturers to develop new vaccines and new vaccine formulations that are either thimerosal-free or contain only trace amounts of thimerosal as a preservative. Great progress has been made in this regard. Manufacturers have been able to accomplish this goal through changing their manufacturing processes, including a switch from multi-dose vials, which generally require a preservative, to single-dose vials or syringes. Since 2001, all vaccines manufactured for the U.S. market and routinely recommended for children 6 years of age have contained no thimerosal or only trace amounts, with the exception of inactivated influenza vaccine. In addition, all of the routinely recommended vaccines that had been previously manufactured with thimerosal as a preservative (some formulations of DTaP, *Haemophilus influenzae b* conjugate (Hib), and hepatitis B vaccines) had reached the end of their shelf life by January 2003.

Inactivated influenza vaccine was added to the routinely recommended vaccines for children 6 to 23 months of age in 2004. FDA has approved thimerosal preservative-free formulations (containing either no or only trace amounts of thimerosal) for the inactivated influenza vaccines manufactured by Sanofi Pasteur and Chiron. These influenza vaccines continue to be marketed in both the preservative free and thimerosal-preservative containing formulations. In addition, in August 2005, FDA licensed GlaxoSmithKline's inactivated influenza vaccine, which contains 1.25 micrograms mercury per dose. Of the three licensed inactivated influenza

vaccines, Sanofi Pasteur's Fluzone is the only one approved for use in children 6-23 months of age. The amount of thimerosal preservative-free vaccine that is available based on current manufacturing capacity is below the number of doses needed to fully vaccinate this age group. FDA is in discussions with manufacturers of influenza vaccine regarding their capacity to further increase the supply of preservative-free formulations.

Prior to the initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury from routine childhood vaccinations during the first six months of life was 187.5 micrograms. With the introduction of thimerosal-preservative-free formulations of DTaP, hepatitis B, and Hib, the maximum cumulative exposure from these vaccines decreased to less than three micrograms of mercury in the first 6 months of life. With the addition of influenza vaccine to the recommended vaccines, an infant could receive a thimerosal-preservative-containing influenza vaccine at 6 and 7 months of age. This would result in a maximum exposure of 28 micrograms from vaccines routinely recommended in the first 7 months of life, a level well below the EPA's exposure guidelines for methylmercury.

The Immunization Safety Review Committee of the Institute of Medicine (IOM) completed two reviews of studies addressing a potential link between thimerosal containing vaccines and autism. The first IOM review was conducted in 2001. Based on the data then available, the IOM concluded the body of data was inadequate to either accept or reject a causal relationship between thimerosal-containing vaccines and neurodevelopmental disorders, including autism. Three years later, in 2004, the IOM Immunization Safety Review Committee, prompted by the accumulation of considerable new data, again reviewed this issue of a potential causal relationship between thimerosal-containing vaccines and autism. Based on a review of this full body of data, which included epidemiological studies from the United States, Denmark, Sweden, and the United Kingdom, the Committee summed up its findings: "Thus, based on this body of evidence, the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism."

CBER has succeeded in markedly reducing childhood exposure to mercury from vaccines and continues these efforts. With the exception of the inactivated influenza vaccine, all vaccines manufactured for the U.S. market and routinely recommended for children ≤ 6 years of age contain no thimerosal or only trace amounts. In addition, all hepatitis vaccines manufactured for the U.S. market for individuals of all ages contain either no thimerosal or only trace amounts, and DT, Td, and Tetanus Toxoid vaccines are now available in formulations that contain no thimerosal or only trace amounts. Furthermore, all new vaccines licensed since 1999 are free of thimerosal as a preservative. A table listing vaccines, preservative contents, and manufacturers can be found on FDA's Web site: www.fda.gov/cber/vaccine/thimerosal.htm.

Biological Safety Activities

Ensuring the safety of biological products is a primary focus of CBER's mission. A major advance toward that goal has been the issuance and implementation of two essential guidances: 1) Pharmacovigilance Planning, and 2) Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. These guidances have played a key role in providing clear scientific direction to sponsors, particularly when their license applications approach approval and post-licensure (also known as "phase 4") studies are being considered. Post-licensure studies may be needed to broaden the base of safety information when pre-licensure clinical trials have excluded potential participants based on age, pregnancy, disease, prior vaccination history, concomitant medications, and other factors.

Collaborating with FDA's Center for Devices and Radiological Health's (CDRH) Medical Product Surveillance Network program (MedSUN), CBER is initiating a pilot study of active surveillance in participating healthcare facilities, particularly hospitals, for adverse events related to tissue transplantation. Active surveillance provides more reliable and complete information on health outcomes and adverse events than can be captured through passive surveillance. A questionnaire and training program have been developed for this pilot study. The initial goal is to enroll 9 MedSUN hospital sites in a 12-month pilot project. MedSUN has been valuable in providing data that have led to increased safety of FDA-licensed devices.

Accelerated reporting of adverse events of interest by applicants beginning at or near the time of licensure has been implemented for several newly licensed vaccines. This approach focuses on adverse events that would not normally meet the criteria for accelerated ("15-day") reporting. Rather than reporting such adverse events every 3 months to FDA, these are instead reported monthly. This allows for more rapid assessment and analysis, with the potential for earlier detection of safety issues and earlier action to minimize risks. In addition, the sponsor receives from FDA on an expedited schedule publicly releasable data on adverse event reports that were submitted directly to FDA and of which the sponsor had been unaware. Thus there is a synergistic two-way exchange of information, benefiting the consumer.

Human cells, tissues, and cellular and tissue-based products (HCT/Ps) are regulated solely under section 361 of the Public Health Service (PHS) Act and applicable regulations in Part 1271 if the product meets all of the criteria described in 21 CFR 1271.10 (http://www.fda.gov/cber/rules/gtp.htm). An HCT/P that falls into this category is referred to as a "361" HCT/P.

Adverse reaction reporting for "361" HCT/Ps, other than reproductive tissues, is required under 21 CFR 1271.350 as of May 25, 2005, the effective date of the Current Good Tissue Practices final rule (http://www.fda.gov/cber/rules/gtp.htm). In addition, CBER may receive reports of adverse reactions through various sources, either outside the agency or from other FDA personnel and government organizations.

Examples of some "361" HCT/Ps when all the criteria in 1271.10 are met include: amniotic membrane when used alone or without added cells; bone; cartilage; cornea; fascia; ligament; pericardium; peripheral or umbilical cord blood stem cells for autologous use or use in a first or second degree blood relative; sclera; skin; tendon; vascular graft; heart valves and dura mater. To ensure that the responsibilities for addressing reported adverse reactions associated with HCT/Ps are clearly established, CBER has formed a Tissue Safety Team (TST) to monitor these adverse reaction reports and to coordinate any related activities. CBER tracks and monitors all adverse reaction reports received (regardless of the format or reporting mechanism used) and initiates and coordinates investigations as appropriate. The initial CBER point of contact will communicate, as appropriate, to other points of contact in the Tissue Safety Team. Coordination with other CBER or FDA units will be conducted as appropriate.

CBER Outreach Update

CBER's outreach efforts during FY 2005 focused on improving the Center's communication with stakeholders. CBER's outreach program reaches tens of thousands of stakeholders annually, both directly and indirectly, including consumers, health care professionals, regulated industry, members of Congress, and the media.

During FY 2005, CBER improved the organization and quality of information on its Web site, which serves as a focal point for obtaining information from the Center on regulations, policies, important emerging issues, and product approvals. There were nearly 14 million visits to the site during FY 2005, averaging approximately 40,000 visits per day. The Center also maintains three automated e-mail distribution lists, which now total more than 9,100 subscribers. These electronic "listservs" allow CBER to distribute information proactively, reaching a wide audience quickly and efficiently.

Over the past several years, CBER has enjoyed a successful exhibit program, and FY 2005 was no exception. The Center participated in many conferences and workshops, reaching a vast array of constituents, including those working in regulated industry, counterterrorism research, infectious diseases and infection control, and parents' groups (see Appendix B).

CBER held several workshops in FY 2005, intended to provide important information to researchers and regulated industry on key topics related to product development and licensure. CBER also conducted information-sharing liaison meetings with trade associations and developed several co-sponsorship agreements for workshops as avenues for disseminating important regulatory and policy information.

The Center conducted targeted outreach to regulated industry and health care provider organizations on several new publications and rules published during FY 2005. In addition, CBER contributed a number of important updates on product approvals and safety information to FDA Patient Safety News, a monthly broadcast produced by the agency and delivered to hospital networks around the country.

CBER Exhibit Program - FY 2005

Meeting	Dates
American Association of Blood Banks Baltimore, MD	October 23-26, 2004
American Society for Microbiology, BioDefense Research Meeting Baltimore, MD	March 20-23, 2005
BioDefense Vaccine & Therapeutics Alexandria, VA	April 18-20, 2005
FDA Science Forum Washington, DC	April 27-28, 2005
National Foundation for Infectious Diseases, Conference on Vaccine Research Baltimore, MD	May 10-11, 2005
NIH Health Expo Wheaton, MD	May 15, 2005
Association for Professionals in Infection Control and Epidemiology Baltimore, MD	June 19-23, 2005
Drug Information Association Meeting Washington, DC	June 26-29, 2005
Maryland Parent Teacher Association Meeting Baltimore, MD	July 30, 2005
NATCO The Organization for Transplant Professionals 30th Anniversary Meeting	July 31- August 3, 2005
American Association of Tissue Banks Annual Meeting Hollywood, FL	September 17-20, 2005

IMPROVING PRODUCT QUALITY, SAFETY, AND AVAILABILITY THROUGH BETTER MANUFACTURING AND PRODUCT OVERSIGHT

Improve Assurance of TSE Safety for Biological Products

The FDA has continued to engage in many activities to enhance the safety of the blood supply by reducing the risk of transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood and blood products. As a precautionary measure, the FDA has had a long-standing practice of recommending the deferral of certain blood donors at increased risk of exposure to vCJD due to significant dietary exposure to beef in high-risk European countries. The FDA has also recommended deferral of donors that have either received a transfusion in the United Kingdom, or donors that have used bovine insulin from the United Kingdom. In addition, FDA seeks expert advice and review of its policies from its Transmissible Spongiform Encephalopathies (TSE) Advisory Committee (TSEAC).

During the past fiscal year, the U.S. Department of Agriculture (USDA) reported the first case of bovine spongiform encephalopathy (BSE) to be recognized in a U.S.-born cow (a previous case in 2003 affected a Canadian-born cow exported to the United States and diagnosed here). More than 550,000 cattle examined by the USDA tested negative for the abnormal protein diagnostic for BSE. CBER staff have been working with others in the FDA to minimize potential exposures to the infectious BSE agent through medical products manufactured with bovine materials.[27]

Given two reports of probable transfusion-transmitted vCJD in the United Kingdom in 2004, FDA asked for TSEAC's advice regarding broadening the scope of donor deferrals for vCJD risk.

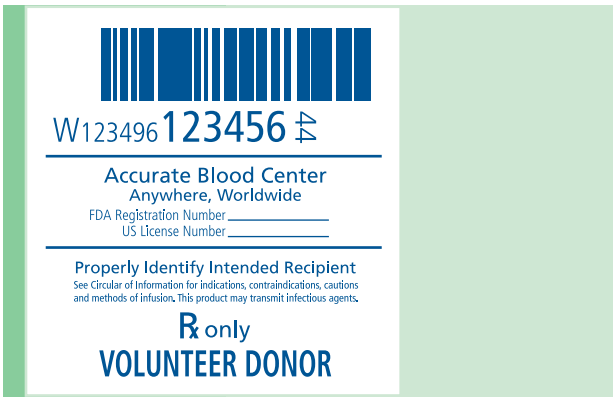
At the TSEAC meeting in February 2005, FDA shared with the committee a concern about the growing number of vCJD cases recognized in France—now up to 14—far more than any other country except the United Kingdom. The FDA requested advice on whether to recommend deferral of blood donors with a history of blood transfusion in France, as FDA already does for donors transfused in the United Kingdom. A majority of TSEAC members advised FDA to take that step for donors transfused in France but not in other countries (except the United Kingdom.) At the same meeting, consistent with FDA's commitment to using a risk-based approach in addressing regulatory decisions, CBER presented a computer-assisted probabilistic model for estimating possible risk of transmitting vCJD to certain recipients of human-plasma-derived coagulation factors. The TSEAC endorsed the general modeling approach and agreed with FDA that the complexity of the analysis and the substantial uncertainties regarding several important parameters in the model make it difficult to estimate the overall risk with confidence. CBER is continuing to develop this model.

Bar Code Label Requirements

The FDA regulations require that certain human drug and biological product labels contain a bar code consisting of, at a minimum, the National Drug Code (NDC) number. Bar codes will allow health care professionals to use bar code scanning equipment to verify that the right drug (in the right dose and right route of administration) is being given to the right patient at the right time. This new system is intended to help protect patients from preventable medication errors in hospitals and health care settings. FDA issued draft

guidance for industry on June 7, 2005. The guidance explains in question-and-answer format how the bar code label requirements apply to specific products or circumstances. The questions are based on those posed to the Agency since the final rule was published in February 2004.

The questions and answers cover information such as, what types of firms are subject to the bar code rule, exemptions, and implementation dates, quality, appearance, and placement of the bar code. For a complete list of questions and answers, the draft guidance can be found at http://www.fda.gov/cder/guidance/6383dft.htm#_Toc102987207.



CGMPs: Council on Pharmaceutical Quality

In September 2004, the Current Good Manufacturing Practice (CGMP) Steering Committee issued the final report of the Agency's two-year "Pharmaceutical CGMP's for the 21st Century: A Risk-Based Approach" initiative. The committee reported that to facilitate FDA's modernization of the regulation of pharmaceutical manufacturing and product quality, the FDA Management Council had established a Council on Pharmaceutical Quality to implement the results of the initiative.

The Council serves as the guiding body on activities and policy development related to the modernization of the regulation of cross-center and Office of Regulatory Affairs (ORA) pharmaceutical manufacturing and product quality. The Council on Pharmaceutical Quality also serves as a resource to the FDA Management Council and to the FDA in general, on matters relevant to this subject.

CBER is represented on the Council and on many working groups that are actively implementing the various activities, such as finalizing the draft guidance to industry on "Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations" and modification of the CGMP regulations governing human and animal pharmaceutical products, including biological drug products.

TRANSFORMING FDA BUSINESS OPERATIONS, SYSTEMS AND INFRASTRUCTURE TO SUPPORT FDA'S MISSION IN THE 21st CENTURY

Review Management Initiatives

The Review Management staff supports the CBER review community with processes and tools to maximize review efficiency and completeness. Review Management staff participate in the Center's outreach efforts, including presentations for industry that focus on the review process within the Agency.

The monthly Review Management Updates continue to be a successful tool for keeping the CBER review community updated on the latest regulations, guidance documents, and standard operating procedures and policies (SOPPs). The presentations were expanded to include those from other centers. Presentations this year included:

- Pediatric Research Equity Act (PREA)
- Resource reporting system (RRS)
- Overview of CBER's Office of Compliance and Biologics Quality (OCBQ) reorganization
- Memoranda of understanding (MOUs) and other agreements
- Physician's labeling rule and electronic labeling
- Regulatory SOPP development and guidance document development

Additional personnel were added to the Review Management staff to enhance our capacity to work in standards development in both electronic submissions and other data standards. Staff currently works closely with Agency, Department, and outside standard-setting organizations in the development of policies and procedures.

The Device Review Subcommittee of the Review Management Coordinating Committee continues to work closely with CDRH to harmonize review processes that reflect the MDUFMA goals. Review Management staff with contributions from review Offices are working diligently to have all review templates available to the review community by spring 2006. The IND clinical and statistical review templates are available for reviewers. The BLA clinical review template and the IND chemistry, manufacturing, and control review template are in the last stages of development with information technology staff.

New initiatives undertaken by Review Management include:

- Development of a program to evaluate and improve control of organizational data systems;
- Review of existing subcommittees and working groups to ensure efficient and consistent consideration of CBER's business processes, both paper and electronic;
- Revision of business processes to include harmonization and consistency with the GRMPs for PDUFA products guidance document published in April 2005;
- Preparations for the reevaluation and refinement of the managed review process that will be initiated in 2006; and
- Establishment of business processes for:
  - Animal component database to capture information related to animal components submitted in investigational and marketing applications/notifications; and
  - Emergency use authorizations administrative procedures for the use of an unapproved product or for the unapproved use of an approved medical product based on a declaration of an emergency by the DHHS Secretary.

Management Initiatives at CBER

Leadership and Management Competencies

In FY 2005, CBER developed leadership and management competencies for supervisory staff so that it is trained to lead and manage the high-quality and diverse workforce of the Center. CBER uses the FDA's managerial job performance model to train first- and second-level leaders and managers, and the federal government's executive core qualifications to develop Senior Executive Service (SES) leaders and managers. This accomplishment integrates and supports the

President's management agenda and HHS department-wide management objectives. CBER is developing a competency-based training and development program to address "Developing and Retaining Talent," one of the cornerstones of human capital management. This initiative supports CBER's mission and serves as the foundation for the Center's staff training and development.

Quality Assurance

The Quality Assurance staff (QAS) serves as a Center-level mediator for dispute resolution and an objective resource for the ongoing review and evaluation of Center programs and operations.

As part of CBER's strategic plan for 2006, the Center has reaffirmed its commitment to assure quality in the performance of all core functions. To this end, a variety of quality assurance activities are being conducted for many of CBER's research, review, and compliance activities.

The QAS supports the office-level QA activities, assists in the identification of problem areas, and helps to identify potential solutions. The QAS also works with the Associate Director for Review Management to monitor implementation and the impact of changes in the Managed Review Program and provides an ongoing evaluation of CBER's efforts to meet relevant performance goals for specific product categories. In FY 2005, as part of CBER's ongoing quality assurance efforts, three Refuse-to-File and Clinical Hold meetings were held, and a fourth meeting was cancelled because of large-scale deployment of Center staff for Hurricane Katrina relief.

In FY 2005, the Center laboratory quality manager within the QAS (as well as three office quality managers and additional lab quality system staff) continued to lead the Center's efforts to gain laboratory accreditation. Their FY 2005 accomplishments include:

- Extensive evaluation, testing, and upgrade of a laboratory quality database software to manage multiple linked databases used in logging, tracking, and trending lab quality system information;
- Training of Center personnel to create customized reports from data in the lab quality database and to customize user interfaces of the laboratory quality database software;
- Providing access to multiple standards documents for reference during design and implementation through the Center's computer network;
- Updating of the Center Laboratory Quality Policy Manual; and,
- Progress toward completion of Center Laboratory Quality Procedures Manual.

To date, 160 documents have been completed including 70 office, division or lab-specific test methods and work instructions. It is anticipated that this laboratory accreditation effort will continue throughout FY 2006.

The Associate Director for Quality Assurance also serves as the CBER ombudsman and the Center's product jurisdiction liaison. The ombudsman position in CBER was established to investigate and act on complaints regarding the CBER regulatory review processes and to provide an effective informal process for resolution of regulatory or scientific problems that cannot be resolved by other means. In instances where an informal process is inadequate, the CBER ombudsman may serve as the mediator or arrange for mediation to conduct the formal dispute resolution process as defined by FDAMA.

In FY 2005, CBER received one formal dispute resolution request, which was addressed in accordance with the time frames specified by FDAMA, and an equitable agreement was reached. In addition, CBER received approximately two informal requests per week for assistance from outside the Agency. Of the informal requests, 21 required a substantial level of intervention or mediation. Nine of these requests related to scientific/regulatory disagreements, 7 involved high-level policy issues, 4 were related to product jurisdiction, and 1 was compliance related.

In addition, the CBER ombudsman handles complaints and questions about inter- and intra-center product jurisdiction and serves as a member of the Tissue Reference Group. With respect to inter-center jurisdiction in FY 2005, more than 30 Requests for Designation were received through the FDA Office of Combination Products. Many of these requests related to combination products that included a biologic and device, biologic and drug, or drug and device component, as well as products that contain a human tissue component in combination with a regulated article. Informal jurisdiction questions increased, with an average of 10 per month.

Emergency Preparedness and Response to Crises

People need quick access to blood products, vaccines, snakebite treatments, and many other biological medical products in the event of a natural disaster (e.g., hurricane, flood, earthquake) or a man-made event (e.g.,

terrorist attack). Extensive advanced planning for the "what if" situations is the only realistic way to ensure that first responders and individuals in the affected area will have the necessary biological products to deal with an emergency. CBER is proud of its role as an integral part of the national and HHS emergency response team. The Office of the Center Director leads our emergency preparedness/response activities. Experience continues to demonstrate that our decisions ahead of the emergency and our actions in response to crisis are essential to protect the public.

Much of this critical "be prepared" work is part of our routine, as our medical, scientific, compliance, and information technology professionals serve as active contributors to the development of national, HHS, and FDA preparedness efforts. For example, in 2005 we contributed to the development of the new Interim National Infrastructure Protection Plan and to the FDA-wide Emergency Response Plan. These plans shape the overall public health protection efforts of the federal government.

We tested our emergency response and communications capabilities during exercises such as the April 2005 Top Officials III (TOPOFF III) exercise, which simulated a massive explosion in Connecticut and the dispersal of plague bacteria in New Jersey. The Center supplied a "trusted agent" to help plan this national event that included state and local authorities, as well as top personnel from every sector of the federal government. Our many TOPOFF III participants within CBER quickly developed simulated guidance documents and press statements concerning the deferral or use of blood, blood products, and human tissues for transplantation, just as we would have done in a real emergency.

The Center's participation in emergency preparedness activities and our quick response to real emergencies demonstrates the contribution of our strong regulatory science base in national public health infrastructure protection efforts.

During the emergency situations caused by Hurricanes Katrina and Rita, CBER put its proactive planning and exercise experience to use in the recovery efforts. We worked with the AABB Inter-organizational Task Force on Domestic Disasters and Acts of Terrorism to gather information on blood supply/availability, to develop public messages about needed blood donations, and to provide advice to blood establishments that had lost electrical power to their storage facilities. The Center facilitated the supply of snakebite treatments to hospitals when the media began to report instances of cottonmouth snakes being washed into populated areas, so that these products would be available if needed within the recommended 6 hours time frame in which to treat snakebite. Immediately after the hurricanes, and in the weeks that followed, CBER responded to after-hours calls for advice and assistance from other federal/state agencies and from regulated industry on topics ranging from storage of temperature-sensitive products to alternate sources of vaccines and immunoglobulins to protect people in the flood-ravaged areas.

Globalization of Public Health and Product Development: International Activities Highlights

International Activities Highlights

The significance of the international dimension to the work of CBER/FDA has grown over recent years, as underscored by FY 2005 events and activities. The events of the 2004-2005 influenza season precipitated by enforcement actions against a manufacturing site abroad, the troubling outcomes of the X-linked Severe Combined Immunodeficiency disorder (X-SCID) gene therapy trials in Europe, the continuing concerns regarding vCJD transmission with their geographic outlines, and the looming threat of pandemic influenza as manifested in the spreading avian influenza incidence in humans, all stand in testimony to this fact. In these high-profile events, as well as more routine program work, the center experienced a greater integration of the international dimension into the work processes of the Center. As noted in last year's report, communication and cooperation with CBER's foreign regulatory counterparts and with international and nongovernmental organizations have proven increasingly critical to the success of the Center's mission.

World Health Organization (WHO)/Pan American Health Organization (PAHO) Activities

The Center is currently in its second term as a designated PAHO/WHO Collaborating Center for Biological Standardization, a standing that reflects the significance the Center places on its engagement with WHO. Through scientific expert consultations and laboratory collaborations, CBER staff continues to make notable contributions to the standard-setting work of WHO as mandated in its charter. In FY 2005, CBER engaged with WHO in activities too numerous to itemize, but included technical efforts specific to: regulatory requirements for human cells and tissues, International Nonproprietary Names for

gene therapy products, neurovirulence testing of live vaccines, specifications for live attenuated rotavirus vaccines, requirements for Diphtheria, Tetanus, and whole cell Pertussis vaccines and Diphtheria, Tetanus, acellular Pertussis vaccines, xenotransplantation regulatory considerations, new vaccine delivery systems, tuberculosis vaccines, post-licensure surveillance, quality and preclinical safety evaluation of DNA vaccines, standardization and control of rabies vaccines for humans, specifications and validation of HIV/AIDS diagnostic technologies, and tissue infectivity distribution in TSEs.

The Center continued to provide leadership in key strategic committees of WHO, including the Global Vaccine Safety Advisory Committee, the Expert Committee on Biological Standardization, and the Global Vaccine Research Forum. The Center also was active in the planning for the 2006 biennial WHO International Conference of Drug Regulatory Authorities to be held in Seoul, Korea, which will include an open plenary specific to biologics.

Bilateral Information Sharing Agreements

In FY 2005, the Agency continued in its leveraging strategy first enunciated in 2003 to forge confidentiality agreements with strategic foreign regulatory counterparts to effect and enhance regulatory cooperation. Several new agreements were finalized, and earlier agreements saw increased operational exchanges. CBER both initiated and responded to requests for information exchange from counterpart agencies in contexts ranging from inspectional issues, to data interpretation, to surveillance signals. Other activities undertaken in FY 2005 included the hosting of several visits, both long-term and short-term, from the European Medicines Agency (EMEA); participation of a CBER staff in an EMEA ad hoc expert group meeting; initiation of a pharmacogenomics dialogue between EMEA and the FDA Interdisciplinary Pharmacogenomic Review Group (IPRG) of which CBER is a member; continued work on the inspectional cooperation with SwissMedic; and dialogue with Health Canada as both agencies addressed regulatory frameworks for tissues and related products. Utilization of these agreements has proven to be value-added to the range of the Center's responsibilities.

International Partnering

The Center has also availed itself of opportunities to partner with other regulators and scientific bodies to maximize both outreach and input on important scientific issues.

For the first time, CBER co-sponsored with the National Institute for Biological Standards and Control, and hosted in the United States, the co-scheduled International Working Group on the Standardization of Genomic Amplification Techniques for the Virological Safety Testing of Blood and Blood Products, and the International Plasma Fractionation Association and Paul Ehrlich Institute Nucleic Acid Testing Workshop on Surveillance Testing and Screening of Blood-Borne Pathogens. CBER provided leadership and funding as a strong signal of its support for this ongoing activity.

CBER joined CDER in co-sponsoring with the European Medicines Agency the 2005 Paternal Drug Association (PDA) Viral Safety Conference in Bethesda, MD. The theme of the conference was, "Updating the Strategy for the 21st Century." The Conference addressed current trends and initiatives among the industry and regulatory authorities, and how these trends and initiatives are expected to impact viral safety concerns in drug product manufacturing and licensing. Discussion focused on TSE safety issues and developments as well as topics related to viral safety. Other international meetings which CBER co-sponsored in FY 2005 included: the "Gene Therapy: State of the Art" conference in London, England, co-sponsored with the Royal Society of Medicine and the International Association for Biologicals; the Eighth U.S.-Japan Cellular and Gene Therapy Conference on RNA Therapy held by the U.S.-Japan Cooperative Program for Recombinant DNA Research, co-sponsored with the Ministry of Education, Culture, Sports, Science and Technology of Japan; and the Fifth Annual Somatic Cell Therapy Symposium co-sponsored with the International Society for Cell Therapy. The Center's scientists have also successfully established a number of research collaborations with Russian and ex-Soviet scientists under the federal Biotechnology Engagement Program, directed at critical public health challenges.

New Leveraging Initiative: PIC/S

One strategic directive stemming from the Agency's 2003-2004 "Pharmaceutical CGMPs for the 21st Century" initiative was to pursue membership in the international Pharmaceutical Inspection Cooperation Scheme (PIC/S). The vision for FDA's participation in this cooperative arrangement is one in which inspectional resources can be leveraged by bringing to bear inspectional information from other regulators as a component of a larger risk-based strategy. Over the course of FY 2005, CBER participated in the detailed work needed to prepare the Agency's application to join the PIC/S. The application was submitted in the latter part of FY 2005. In addition,

CBER participated in meetings of several PIC/S Expert Circles, including the Expert Circle on Human Blood and Tissue, by special invitation.

International Conference on Harmonization (ICH)

The ICH is a unique project that brings together the regulatory authorities and pharmaceutical industry experts from Europe, Japan, and the United States to discuss scientific and technical aspects of product registration. CBER joins CDER as members to the ICH Steering Committee and provides technical representation to the various types of working groups that undertake the work of ICH: expert working groups, implementation working groups, informal discussion groups, brainstorming groups, etc.

Of particular note specific to CBER was the work of its experts in the Gene Therapy Discussion Group over the course of FY 2005 in planning for a public one-day workshop on oncolytic viruses in November 2005. The workshop is to be held in conjunction with ICH expert working groups and steering committee meetings in Chicago, IL. The objectives of the workshop are to identify and discuss issues relevant to clinical development of oncolytic viruses including safety.

Fiscal Year 2005 saw further advances of the topics Q8 (pharmaceutical development), Q9 (quality risk management) and the potential Q10 (manufacturing quality systems), first conceptualized by FDA as components of its international strategy within the Pharmaceutical CGMPs for the 21st Century initiative. Q8 was finalized, Q9 reached the draft for comment stage ("Step 2"), and discussion on the potential Q10 topic continued. Beginning in 2003, through the winter of 2004, an extended review of the ICH construct and its processes took place under the umbrella concept of the "Future of ICH." The self-examination addressed the process for the selection of new topics, increasing the efficiency of working groups, the frequency of meetings, improving implementation processes, and membership. As part of its consideration of future directions, two sequential pharmacovigilance brainstorming sessions were held to identify potential new topics; in the same vein, agreement was reached on holding a biotechnology brainstorming session and a pharmacogenomics brainstorming session at the November 2005 meetings. It is expected that by the first meeting in FY 2006, the ICH Steering Committee will identify several new topics to take up.

International Outreach

Members of the CBER staff routinely participate in international scientific meetings where they share both their scientific and regulatory expertise. At the invitation of many organizations and countries, CBER staff interacts via presentations, workshops, and dialogue as time and resources allow. A sample of these activities in FY 2005 includes the following:

- Sessions at the International Society for Cellular Therapies Current Good Tissue Practice Workshop and an "Ask the Experts" session in Vancouver, Canada with presentations focused on the new 21 CFR Part 1271 regulations for Human Cells, Tissue, and Cellular and Tissue-Based Products and its potential effect on manufacturers of peripheral and cord blood stem cells;
- The International Symposium for Current Issues on Xenotransplantation hosted by the Korean FDA with a talk entitled, "Current Issues and International Overview of Xenotransplantation," and a follow-up seminar entitled, "Overview of Xenotransplantation Regulation in the United States";
- The University of Rhode Island's 11th Annual "Surviving the Challenges of FDA and Other Regulatory Authorities' GMPs," in Prague, Czech Republic, with two presentations: "CBER Compliance Update," and "Risk and Compliance: The Meaning of Risk;" and
- The "Third International Meeting on Oncolytic Viruses as Cancer Therapeutics," in Banff, Alberta, Canada with a presentation entitled "Animal Models for Testing Safety of Oncolytic Viruses: Preclinical Expectations for IND Submission."

Global Vaccine Development

The Center's ongoing efforts to address the range of international regulatory needs related to vaccines that target diseases of global significance dovetailed in FY 2005 with the need to take concrete steps to advance the planning and preparation for an influenza pandemic. The concept of an influenza pandemic is an inherently global one, from the likely emergence of a deadly strain in a distant site, to the subsequent expected global spread, to the development, production, and distribution of medical preventions and interventions to save lives in its wake.

CBER initiated dialogues with counterpart regulators with whom the Agency has confidentiality agreements to discuss the relative approaches to the use of pandemic strains in the formulation of influenza vaccines and regulatory mechanisms to facilitate the licensure of these vaccines. These dialogues are ongoing.

Also in FY 2005, CBER continued to engage substantially with WHO and agreed to support a WHO meeting of regulatory authorities from countries with the capacity for developing and/or manufacturing pandemic flu

vaccines to: 1) share current regulatory perspectives and approaches regarding clinical trial, preclinical, and manufacturing information desirable for approval and release of candidate pandemic vaccines of various types (including inactivated, live attenuated, cell culture and recombinant vaccines, with or without adjuvants); 2) identify regulatory inconsistencies/disharmonies that may serve as impediments to the expeditious development and production of pandemic flu vaccines; 3) identify and prioritize possible areas in which regulatory harmonization and/or increased regulatory cooperation could achieve a reduction of these impediments; and 4) consider a strategy for moving forward in specific high-priority areas.

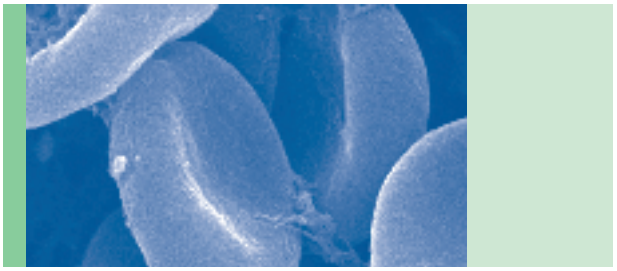
Apart from vaccine activities and efforts specific to influenza, CBER continued its efforts to more broadly provide effective regulatory and consultative assistance to developing country regulators on vaccine issues. The Center has joined with the WHO Developing Country Vaccine Regulatory Network to offer a joint conference/workshop to discuss the regulatory challenges of producing, testing, and introducing HIV vaccines in Asia. The conference/workshop was scheduled to take place in Bangkok, Thailand in November 2005.

Global Collaboration for Blood Safety

The Center continued to support the partnership of the Global Collaboration for Blood Safety (GCBS), with CBER's Director of the Office of Blood Research and Review serving in his third year as chair. The GCBS was created by WHO in 2000 to implement World Health Assembly Resolution 48.27 (1995), which contained a commitment to international collaboration for blood transfusion safety. According to its terms of reference, GCBS was constituted as "a voluntary partnership of internationally recognized organizations, institutions, associations, agencies, and experts from developing and developed countries sharing the expertise, identifying problems, seeking solutions, and working toward the common goal of global blood safety as equal collaborative partners. WHO is a participant of GCBS and also provides its secretariat."

The GCBS is a forum that facilitates international collaboration in blood safety and availability through dialogue, nonbinding recommendations and cooperative work. The fifth plenary meeting of the GCBS was held in Geneva, Switzerland on November 10-12, 2004. Approximately 50 people attended the meeting, representing a spectrum of organizations, institutions, and associations with international interests related to global blood safety.

One important outcome of the plenary meeting was international support for and passage of a World Health Assembly Resolution (WHA 58.13) to establish an annual World Blood Donor Day. The resolution further urged member states to take a set of actions in support of



blood safety and availability, including establishment of quality processes for blood policy and decision-making. CBER played a significant role in the first World Blood Donor Day by assisting a U.S. contractor in the development of suitable communication tools that were used by the major blood organizations. Additionally, FDA and DHHS were the leaders in providing advocacy for the expansion of World Health Assembly (WHA) 58.13 to encompass support for quality processes in decision making related to national blood systems. We have also been highly active in assisting WHO to develop standards for blood and plasma, including guidance documents, reference reagents and international standard reagents. The U.S. regulatory system already incorporates the quality processes that are advocated worldwide in the World Health Assembly Resolution.

Harmonization Efforts and International Standards in Blood/Blood Products

To improve regulatory harmonization, CBER joined the International Society on Thrombosis & Haemostasis (ISTH)-WHO Liaison committee that will select and prioritize the development of international potency reference standards for coagulation products. The Center staff presented the FDA perspective on harmonization of plasma requirements at the Plasma Protein Therapeutics Association (PPTA) Plasma Protein Forum in June 2005. In September 2005, at PPTA's Emerging Infectious Roundtable 2, CBER staff discussed opportunities to increase early detection and evaluation of new threats of infectious agents to the safety of blood and plasma derivatives. The Center sent an observer to the Group of Experts 6B committee of the EMEA in September 2005 to participate in discussions about standards for plasma derivatives and pyrogen testing in Europe. Such discussions will facilitate potential harmonization of standards for U.S. products and tests. In addition, CBER provided a representative to a jointly sponsored meeting of the European Blood Alliance and America's Blood Centers in July 2005 at which world leaders in blood collection and blood regulation discussed possible approaches to global harmonization of blood standards.

Information Technology Enhancements

The Office of Information Technology (OIT) supports the Center's business processes by providing automated and integrated tools, databases, and systems that enable staff to fulfill CBER's mission. The OIT-CBER implemented a significant technology upgrade in February 2005 for

all CBER systems with the Oracle production database migration to version 9i, which provides increased technical and development advantages, including better security and patch management, XML data features and support, performance enhancements, and support for Oracle Web Portal development.

Another major project was the physical move of all CBER servers to FDA's Network Control Center, which supports the Agency's goal to consolidate and manage IT infrastructure resources for increased efficiencies. In addition, all of CBER's critical IT systems are fully security-certified and accredited, contributing to HHS's goals to meet the President's management agenda objectives. Operations and maintenance activities continue for all production systems as well as enhancements for key projects.

System Upgrades Benefit CBER and CDER

Many CBER systems are also used by CDER to track biologic product applications, meetings, and other regulatory information. Systems were modified specifically to accommodate the 14 new review divisions in 5 offices resulting from the CDER, Office of New Drugs (OND) move to White Oak in September 2005. Several hundred CDER employees were added in CBER's personnel table database and were granted access to CBER systems. OIT-CBER collaborated with CDER business staff over seven months to ensure successful implementation with minimal impact to CBER and CDER reviewers.

Additional IT enhancements in FY 2005 for CBER regulatory management systems include:

- *Biologics Investigational New Drug Management System (BIMS)*
  The Biologics Investigational New Drug Management System (BIMS) supports high-level tracking and summarization of CBER regulatory efforts associated with investigational new drugs (INDs), master files (MF), and investigational device exemptions (IDEs). The system was enhanced to support the review, management and tracking of emergency use authorization (EUA) submissions. Five other software releases were implemented, providing numerous process modifications, including changes for product data-entry, data quality, and handling of original submissions and amendments, which greatly reduced processing time by reviewers. BIMS is used by more than 600 CDER and CBER medical product reviewers;
- *Biologics License Application (BLA)*
  The Regulatory Management System for the Biologics License Application (RMS/BLA) provides an automated system to support the tracking of BLAs, their review, and their associated data. Three major software upgrades were successfully implemented comprising more than 100 user and programmer-generated change requests, 350 data change requests, 2 data migration-related requests, several performance-related enhancements, and 15 special report requests. Among these enhancements were modifications to support MDUFMA, promotional materials review, foreign inspections, routing request capability, and additional search and reporting capabilities;
- *CBER Regulatory Meetings Tracking System (CRMTS)*
  The CBER Regulatory Meetings Tracking System (CRMTS) fulfills the requirements of PDUFA to track industry's requests for formal meetings with the Center and to capture the information necessary to measure performance. Enhancements to the CRMTS included the ability to track meetings related to emergency use authorization (EUA) requests and additional reporting and analysis capabilities;
- *Lot Release System (LRS)*
  The Lot Release System (LRS) supports the processing of lots and issuance of release notifications. The LRS also supports inventory, routing, and laboratory sample tracking. There were two major software releases, consisting of nearly 50 use-requested and programmer-generated improvements. One of the major enhancements, a new Milestones Module for the purpose of tracking and reporting on performance throughout the lot review and release process, will enable the Product Release Branch (PRB) to track and report on time between events and actions taken for a given lot; and
- *CBER's Electronic Document Room (EDR)*
  The Center's Electronic Document Room (EDR) functions as an electronic library for reviewers, distributing and storing electronic submissions of IND, BLA, NDA, 510(k), PMA, regulatory correspondence, and other CBER data. EDR enhancements include the integration of the FDA electronic Common Technical Document (eCTD) review tool that allows for the receipt of eCTD-based submissions, hardware and operating system upgrades, software modifications to the Electronic Secure E-mail system (ESM), ability to receive and extract data from PDF forms received on physical media, capability to process trans-BLA submissions, and PDF link checking software for submission processing.

Supporting eGovernment

Several systems continue to provide electronic access to CBER via the Internet. Both the number of establishments registering electronically, as well as product deviation reports submitted has increased in the past year. During FY 2005:

- 1,922 blood establishments registered via eBER, CBER's electronic Blood Establishment Registration system, representing 70% of all blood establishments registered;
- 938 establishments registered via eHCTERS, CBER's electronic Human, Cell and Tissue Establishment Registration System, representing 47% of all human, cell and tissue establishment registrations; and
- 24,267 electronic Biological Product Deviation Reports, representing 63% of the total submitted biological product deviation reports.

During FY 2005, CBER's EDR supported the following electronic submissions:

- *Original INDs = 56*
- *IND Amendments = 1707*
- *Original BLAs = 12*
- *Supplements, Annual Reports, etc = 742*
- *Amendments = 537*

Contact Us

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www.fda.gov/cber

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fax 301-827-3843 / matt@cber.fda.gov

Ombudsman
301-827-0379 / fax 301-827-2920
lard@cber.fda.gov or balick@cber.fda.gov

Freedom of Information Act (FOIA) Requests
800-835-4709 or 301-827-1800
www.fda.gov/opacom/backgrounders/foiahand.html

VAERS
800-822-7967 / fax 877-721-0366
info@vaers.org / http://Vaers.hhs.gov/
www.fda.gov/cber/vaers/vaers.htm

Genetic Modification Clinical Research Information System (GeMCRIS)
www.gemcris.od.nih.gov

MEDWATCH
800-FDA-1088 or 301-827-7240
fax 301-827-7241 or 800-FDA-0178
www.fda.gov/medwatch/index.html

Biological Product Deviation Reporting
301-827-6220 / bp_deviations@cber.fda.gov
www.fda.gov/cber/biodev/biodev.htm

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BLOODINFO
Includes all blood-related documents.

CBERINFO
Includes TISSUEINFO, BLOODINFO, and all other new CBER documents.

TISSUEINFO
Includes all tissue-related documents

APPENDIX A (CBER Publications)

1. Banks D, Woo EJ, Burwen DR, Perucci P, Braun MM, Ball R. Comparing data mining methods on the VAERS database. *Pharmacoepidemiol Drug Saf*. 14(9):601-9 (2005)

2. Izurieta HS, Haber P, Wise RP, Iskander J, Pratt D, Mink C, Chang S, Braun MM, Ball R. Adverse Events Reported Following Live, Cold-Adapted, Intranasal Influenza Vaccine. *JAMA*. 294(21):2720-2725 (2005)

3. Varricchio F. Vaccine adverse event reporting: the importance of follow-up. *Expert Rev Vaccines*. 4(4):445-8 (2005)

4. Freedman SB, Reed J, Burwen DR, Wise RP, Weiss A, Ball R. Transient Bulging Fontanelle after Vaccination: Case Report and Review of the Vaccine Adverse Event Reporting System. *J Pediatr*. 147(5):640-644 (2005)

5. Porter CM, Bloom ET. Human CD4+CD25+ Regulatory T cells Suppress Anti-Porcine Xenogeneic Response. *Am. J. Transplant*. 5(8):2052-7 (2005)

6. Finlay WJ, Devore NC, Dobrovolskaia EN, Gam A, Goodyear CS, Slater JE. Exploiting the avian immunoglobulin system to simplify the generation of recombinant antibodies to allergenic proteins. *Clin Exp Allergy*. 35(8):1040-8 (2005)

7. Jones-Tower A, Garcia A, Meseda CA, He Y, Weiss C, Kumar A, Weir JP, Merchlinsky M. Identification and preliminary characterization of vaccinia virus (Dryvax) antigens recognized by vaccinia immune globulin. *Virology* 343(1):128-40 (2005)

8. Warfel JM, Steele AD, D'Agnillo F. Anthrax lethal toxin induces endothelial barrier dysfunction. *Am J Pathol*. 166(6):1871-81 (2005)

9. Berthold I, Pombo ML, Wagner L, Arciniega JL. Immunogenicity in mice of anthrax recombinant protective antigen in the presence of aluminum adjuvants. *Vaccine* 23(16):1993-9 (2005)

10. Edghill-Smith Y, Golding H, Manischewitz J, King LR, Scott D, Bray M, Nalca A, Hooper JW, Whitehouse CA, Schmitz JE, Reimann KA, Franchini G. Smallpox vaccine-induced antibodies are necessary and sufficient for protection against monkeypox virus. *Nat Med*. 11(7):740-7 (2005)

11. Meseda CA, Garcia AD, Kumar A, Mayer AE, Manischewitz J, King LR, Golding H, Merchlinsky M, Weir JP. Enhanced immunogenicity and protective effect conferred by vaccination with combinations of modified vaccinia virus Ankara and licensed smallpox vaccine Dryvax in a mouse model. *Virology* 339(2):164-75 (2005)

12. Tomioka K, Peredelchuk M, Zhu X, Arena R, Volokhov D, Selvapandiyan A, Stabler K, Mellquist-Riemenschneider J, Chizhikov V, Kaplan G, Nakhasi H, Duncan R. A multiplex polymerase chain reaction microarray assay to detect bioterror pathogens in blood. *J Mol Diagn*. 7(4):486-94 (2005)

13. Edghill-Smith Y, Bray M, Whitehouse CA, Miller D, Mucker E, Manischewitz J, King LR, Robert-Guroff M, Hryniewicz A, Venzon D, Meseda C, Weir J, Nalca A, Livingston V, Wells J, Lewis MG, Huggins J, Zwiers SH, Golding H, Franchini G. Smallpox vaccine does not protect macaques with AIDS from a lethal monkeypox virus challenge. *J Infect Dis*. 191(3):372-81 (2005)

14. McMahon AW, Bryant-Genevier MC, Woo EJ, Braun MM, Ball R. Photophobia following smallpox vaccination. *Vaccine.* 23(9):1097-8 (2005)

15. Cowley SC, Hamilton E, Frelinger JA, Su J, Forman J, Elkins KL. CD4-CD8- T cells control intracellular bacterial infections both in vitro and in vivo. *J Exp Med.* 202(2):309-19 (2005)

16. Cote TR, Mohan AK, Polder JA, Walton MK, Braun MM. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. *J Am Acad Dermatol*. 53(3):407-15 (2005)

17. Ishii KJ, Ito S, Tamura T, Hemmi H, Conover J, Ozato K, Akira S, Klinman DM. CpG-activated Thy1.2(+) dendritic cells protect against lethal Listeria monocytogenes infection. *Eur J Immunol*. 35(8):2397-2405 (2005)

18. Xie H, Gursel I, Ivins BE, Singh M, O'hagan DT, Ulmer JB, Klinman DM. CpG Oligodeoxynucleotides Adsorbed onto Polylactide-Co-Glycolide Microparticles Improve the Immunogenicity and Protective Activity of the Licensed Anthrax Vaccine. *Infect Immun.* 73(2):828-33 (2005)

19. Gioia CA, de Sousa AB, Cruz SC, Junior FC, Andrade AF, Sassi RM, Frasch CE, Milagres LG. Effect of a booster dose of serogroup B meningococcal vaccine on antibody response to Neisseria meningitidis in mice vaccinated with different immunization schedules. *FEMS Immunol Med Microbiol*. 44(1):35-42 (2005)

20. Frasch CE. Recent developments in Neisseria meningitidis group A conjugate vaccines. *Expert Opin Biol Ther*. 5(2):273-80 (2005)

21. Yang AX, Mejido J, Luo Y, Zeng X, Schwartz C, Wu T, Thies RS, Bhattacharya B, Han J, Freed B, Rao M, Puri RK. Development of a focused microarray to assess human embryonic stem cell differentiation. *Stem Cells Dev.* 14(3):270-84 (2005)

22. Bhattacharya B, Cai J, Luo Y, Miura T, Mejido J, Brimble SN, Zeng X, Schulz TC, Rao MS, Puri RK. Comparison of the gene expression profile of undifferentiated human embryonic stem cell lines and differentiating embryoid bodies. BMC *Dev Biol.* 5:22 (2005)

23. Bloom ET, Epstein SL, Simek SL. Critical Path Workshop on the Development of Cellular and Gene Therapy Products. *Mol Ther.* 12(1):5-8 (2005)

24. Rios M, Daniel S, Stramer S.L., Caglioti S, Wood O, Hewlett I. K. West Nile Virus NAT-Positive Human Plasma Containing WNV-IgM and –IgG Antibodies Can Infect Vero Cells and Human Primary Macrophages in Culture. *Transfusion*. 45S:3A S2-030B (2005)

25. Epstein SL, Kong WP, Misplon JA, Lo CY, Tumpey TM, Xu L, Nabel GJ. Protection against multiple influenza A subtypes by vaccination with highly conserved nucleoprotein. *Vaccine*. 23(46-47):5404-10 (2005)

26. Liu T, Ye Z. Attenuating Mutations of the Matrix Gene of Influenza A/WSN/33 Virus. *J Virol.* 79(3):1918-23 (2005)

27. Farshid M, Taffs RE, Scott D, Asher DM, Brorson K. The clearance of viruses and transmissible spongiform encephalopathy agents from biologicals. Curr Opin Biotechnol. 16(5):561-7 (2005)

APPENDIX B (CBER Major Approvals – FY 2005)

Biologics License Applications

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
ProQuad Measles, Mumps, Rubella and Varicella Virus Vaccine Live	For vaccination against measles, mumps, rubella, and varicella in children 12 months to 12 years of age	Merck & Co, Inc. P.O. Box 4 Sumneytown Pike West Point, PA 19486
Fluarix Influenza Virus Vaccine	For active immunization of adults 18 years of age and older against influenza disease caused by influenza virus types A and B	GlaxoSmithKline Biologicals Rue de l'Institut 89 B1330 Rixensart Belgium
Component of Erytype S Blood Grouping Reagents: Anti-A (Murine Monoclonal); Anti-B (Murine Monoclonal); Anti-A,B (Murine Monoclonal Blend); Anti-D (Monoclonal) (IgM)	To perform a single ABO Grouping and D Typing or label confirmation for donor ABO Grouping and/or D Typing (for exclusive use on the Tango Automated Analyzer)	Biotest AG Landsteinerstrasse 5 D-63303 Dreieich Germany
Anti-Human Globulin Solidscreen II Anti-Human Globulin, Anti-IgG (Rabbit)	To detect the sensitization of Reagent Red Blood Cells by immunoglobulins (for exclusive use on the Tango Automated Analyzer)	Biotest AG Landsteinerstrasse 5 D-63303 Dreieich Germany
Adacel Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Booster immunization against tetanus, diphtheria and pertussis as a single dose in individuals 11 through 64 years of age	Aventis Pasteur Limited 1755 Steeles Avenue West Toronto, Ontario Canada MSR 3T4
Boostrix Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Booster immunization against tetanus, diphtheria and pertussis as a single dose in adolescents 10-18 years of age	GlaxoSmithKline Biologicals Rue de l'Institut 89 B1330 Rixensart Belgium
Gammagard Liquid Immune Globulin Intravenous (Human), 10% Solution	Liquid Preparation of IGIV for Treatment of Primary Immune Deficiency.	Baxter HealthCare Corp One Baxter Way Westlake Village, CA 91362
COBAS AmpliScreen HBV Test Hepatitis B Virus (Hepatitis B Virus/Polymerase Chain Reaction/Blood Cell Derived)	Qualitative in vitro test for the direct detection of Hepatitis B Virus (HBV) DNA in human plasma from donations of whole blood and blood components for transfusion, and source plasma, as well as for testing individual plasma samples from other living donors and organ donors (when specimens are obtained while the donor's heart is still beating)	Roche Molecular Systems, Inc. 4300 Hacienda Drive Pleasanton, CA 94588-2722

Biologics License Applications (Continued)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
Vaccinia Immune Globulin Intravenous (Human)	For the treatment and modification of aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard; eczema vaccinatum; progressive vaccinia; severe generalized vaccinia, and vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions	DynPort Vaccine Company LLC 64 Thomas Johnson Drive Frederick, MD 21702
Menactra Meningococcal Polysaccharide (Serogroups A, C, Y and W-135) Diphtheria Toxoid Conjugate Vaccine	For active immunization of adolescents and adults 11-55 years of age for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, Y and W-135	Aventis Pasteur, Inc. Discovery Drive Swiftwater, PA 18370-0187
Vaccinia Immune Globulin Intravenous (Human)	Treatment and/or modification of the following conditions, which are complications resulting from smallpox vaccination: • Eczema vaccinatum • Progressive vaccinia • Severe generalized vaccinia • Vaccinia infections in individuals who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in individuals who have eczematous skin lesions because of either the activity or extensiveness of such lesions Aberrant infections induced by vaccinia virus that include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard.	Cangene Corp 104 Chancellor Matheson Road Winnipeg, Manitoba Canada R3T5Y3

Biologics License Supplements

(for New Indications, New Routes of Administration, New Dosage Forms, Improved Safety)

Tradename/ Proper Name	Indication for Use	Manufacturer/ License No.
Fluvirin Influenza Virus Vaccine	2005-2006 United States formulation	Chiron Corp 4560 Horton Street Emeryville, CA 94608-2916
FluMist Influenza Virus Vaccine Live, Intranasal	2005-2006 United States formulation	MedImmune Vaccines, Inc. 297 N. Bernardo Ave Mountain View, CA 94043
NovoSeven Coagulation Factor VIIa (Recombinant)	For use in surgical procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX	Novo Nordisk Pharmaceuticals, Inc. 100 College Road West Princeton, NJ 08540
VAQTA Hepatitis A Vaccine, Inactivated	Lowering the age indication for VAQTA from two years to 12 months of age	Merck & Co, Inc. P.O. Box 4, UN-B121 West Point, PA 19486
Fluzone Influenza Virus Vaccine	2005-2006 United States formulation	Aventis Pasteur Inc Discovery Drive Swiftwater, PA 18370-0187
NovoSeveno Coagulation Factor VIIa (Recombinant)	Treatment of bleeding episodes in patients with Factor VII Deficiency	Novo Nordisk Pharmaceuticals, Inc. 100 College Road West Princeton, NJ 08540
Biothrax Anthrax Vaccine Adsorbed	Extension of dating to 36 months	BioPort Corp 3500 N. Martin Luther King, Jr. Blvd Lansing, MI 48906
Varivax Varicella Virus Vaccine Live	Optional second dose for children 12 months to 12 years of age	Merck & Co, Inc. Sumneytown Pike P.O. Box 4 West Point, PA 19486
WinRho SDF Liquid Rho(D) Immune Globulin Intravenous (Human)	To allow a liquid formulation	Cangene Corp 104 Chancellor Matheson Road Winnipeg, Manitoba Canada R3T5Y3

Device Applications

Tradename	Description and Indication for Device	Applicant
Multispot HIV-1/HIV-2 Rapid Test	For the detection and differentiation of circulating antibodies associated with HIV-1 and HIV-2 in human plasma and serum, as an aid in the diagnosis of infection with HIV-1 and/or HIV-2.	Bio-Rad Laboratories 6565 185th Ave., NE Redmond, WA 98052

APPENDIX C (Rulemaking and Guidance Documents–FY 2005)

Rulemaking and Guidance Documents for FY2005

Rulemakings

A. The following proposed and final rules were issued by CBER and published in the *Federal Register* in FY 2005:

- Human Cells, Tissues, and Cellular and Tissue-Based Products; Donor Screening and Testing, and Related Labeling; Interim Final Rule—5/24/2005
- Food and Drug Administration Regulations; Drug and Biological Product Consolidation; Addresses; Final Rule; Technical Amendment—3/24/2005
- Medical Devices; Hematology and Pathology Devices; Reclassification from Class III to Class II of Automated Blood Cell Separator Device Operating by Centrifugal Separation Principle; Proposed Rule—3/10/2005
- Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Proposed Rule and Proposed Order—12/29/2004
- Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement; Final Rule—11/18/2004

B. CBER/Policy Staff was involved in the clearance of the following published proposed and final rules for which other FDA Centers/Offices were the lead:

- Definition of Primary Mode of Action of a Combination Product; Final Rule—8/25/2005

Guidance Documents

(Guidance documents can be viewed at http://www.fda.gov/cber/guidelines.htm)

A. The following guidance documents were issued by CBER and posted and/or published in FY 2005:

- Draft Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods—9/30/2005
- Draft Guidance for Industry: Gene Therapy Clinical Trials–Observing Participants for Delayed Adverse Events—8/23/2005
- Draft Guidance for Industry: Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry—7/19/2005
- Guidance for Industry: Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection—6/23/2005
- Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials—4/29/2005
- Draft Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Automated Blood Cell Separator Device Operating by Centrifugal or Filtration Separation Principle—3/9/2005
- Draft Guidance for Industry: Manufacturing Biological Drug Substances, Intermediates, or Products Using Spore-Forming Microorganisms—2/23/2005
- Draft Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications—2/17/2005
- Guidance for Industry: Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)—11/12/2004

- Draft Guidance for FDA Review Staff and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)—11/8/2004
- Draft Guidance for Industry: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes—10/28/2004
- Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV—10/21/2004
- Guidance for Industry: FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information—10/1/2004

B. CBER/Policy Staff was involved in the clearance of the following published draft and final guidances for which other FDA Centers/Offices were the lead:

- International Conference on Harmonisation (ICH); Guidance for Industry: E2B(R) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports—9/30/2005
- Draft Guidance for Industry: Using Electronic Means to Distribute Certain Product Information–9/29/2005
- Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials—9/19/2005
- Guidance for Industry, FDA Staff, and FDA-Accredited Third Parties: Requests for Inspection by an Accredited Person under the Inspection by Accredited Persons Program Authorized by Section 201 of the Medical Device User Fee and Modernization Act of 2002—9/15/2005
- Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act—9/7/2005
- International Conference on Harmonisation (ICH); Draft Guideline: M5 Data Elements and Standards for Drug Dictionaries—9/2/2005
- International Conference on Harmonisation (ICH); Draft Consensus Guideline: Q9 Quality Risk Management—8/5/2005
- Draft Guidance: Emergency Use Authorization of Medical Products—7/5/2005
- International Conference on Harmonisation (ICH); Guidance for Industry: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process—6/29/2005
- Draft Guidance for Industry: Bar Code Label Requirements–Questions and Answers—6/7/2005
- Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients—5/18/2005
- Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices—5/12/2005
- Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies—4/27/2005
- Guidance for Industry and FDA Staff: Application User Fees for Combination Products—4/20/2005
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format–Content of Labeling—4/20/2005
- Guidance for Industry and FDA Staff: Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product—4/11/2005

- Draft Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics—4/1/2005
- International Conference on Harmonisation (ICH); Guidance for Industry: E2E Pharmacovigilance Planning—3/31/2005
- Guidance for Review Staff and Industry: Good Review Management Principles for PDUFA Products—3/30/2005
- Guidance for Industry: Premarketing Risk Assessment—3/25/2005
- Guidance for Industry: Development and Use of Risk Minimization Action Plans—3/25/2005
- Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment—3/25/2005
- Draft Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials—3/25/2005
- Guidance for Industry: Pharmacogenomic Data Submissions—3/22/2005
- International Conference on Harmonisation (ICH) Guidance for Industry: M2: eCTD Specification; Questions & Answers and Change Requests—3/11/2005
- International Conference on Harmonisation (ICH) Guidance for Industry: E2B(M): Data Elements for Transmission of Individual Case Safety Reports: Questions and Answers (Revision 2)–3/9/2005
- International Conference on Harmonisation (ICH); Draft Guidance on Q8 Pharmaceutical Development—2/8/2005
- Draft Guidance for Industry: Clinical Lactation Studies - Study Design, Data Analysis, and Recommendations for Labeling—2/7/2005
- International Conference on Harmonisation (ICH); Draft Guidance on S8 Immunotoxicity Studies for Human Pharmaceuticals—2/7/2005
- Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees—1/3/2005
- International Conference on Harmonisation (ICH); Guidance for Industry: M-4: CTD–Efficacy: Questions and Answers (Revision 3)—12/22/2004
- International Conference on Harmonisation (ICH); Guidance for Industry: M4: The CTD–General: Questions and Answers (Revision 3)—12/22/2004
- Guidance for Industry and FDA Staff: Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use—11/30/2004
- Guidance for Industry: Continuous Marketing Applications: Pilot 2–Scientific Feedback and Interactions During Development of Fast Track Products Under the Prescription Drug User Fee Act of 1992; Notice of extension of application deadline—11/19/2004
- Guidance for Industry and FDA Staff: Resolution of Disputes Concerning Payment or Refund of Medical Device User Fees Under MDUFMA—11/17/2004
- Guidance for Industry, FDA Staff, and Third Parties: Implementation of the Inspection by Accredited Persons Program Under The Medical Device User Fee and Modernization Act of 2002; Accreditation Criteria—10/1/2004

APPENDIX D (Advisory Committee Meetings–FY 2005)

Advisory Committee Meetings

http://www.fda.gov/cber/advisory/advisory.html

Allergenic Products Advisory Committee

- April 7, 2005
  - Committee Updates: FDA Critical Path Initiative http://www.fda.gov/oc/initiatives/criticalpath/
  - Open Discussion Topics: proposed strategy for the re-classification of Class IIIA allergenic products.

Blood Products Advisory Committee

- October 21-22, 2004
  - Committee Updates: the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) meeting discussion of new variant Creutzfeldt-Jacob disease (vCJD) transmission by transfusion in the United Kingdom and supplemental testing for human immunodeficiency virus (HIV) and hepatitis C virus (HCV); summary of the Plasma Workshop held on August 31-September 1, 2004, draft uniform donor health questionnaire acceptance guidance: review of public comments, and FDA current thinking on monitoring weight in source plasma donors.
  - Open Discussion Topics: re-entry of donors previously deferred for Hepatitis B Core Antigen, Antibody (Anti-HBc) reactivity; potential risk of transmission of Simian Foamy Virus (SFV) by blood transfusions; donor deferral for potential or documented infection with West Nile virus (WNV).
- March 17-18, 2005
  - Committee Updates: summary of the Department of Health and Human Services Advisory Committee on Blood Safety and Availability meeting; summary of the Transmissible Spongiform Encephalopathies Advisory Committee meeting; update on West Nile Virus guidance; summaries of the Critical Path Initiative workshop; update on international agreements.
  - Open Discussion Topics: safety of albumin; rapid freezing of plasma for transfusion; sharing information with the public; the study design for the abbreviated uniform donor history questionnaire.
  - Closed Discussion Topics: site visit report for the Laboratory of Molecular Virology, Division of Emerging Transfusion Transmitted Diseases, Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER).
- July 21-22, 2005
  - Committee Updates: summary of the May 2005 meeting of the Department of Health and Human Services Advisory Committee on Blood Safety and Availability; disseminated intravascular coagulation associated with acute hemoglobinemia following anti-D Immune Globulin Intravenous administration for idiopathic thrombocytopenic purpura; update on safety of albumin; summary of June 2005 workshop on Biological Therapeutics for Rare Plasma Protein Disorders; summary of July 2005 workshop on Leukoreduction; updates on West Nile Virus guidance.
  - Open Discussion Topics: management of donors and units that test positive for Hepatitis B Virus DNA by nucleic acid tests; scientific basis for review of Varicella Zoster Immune Globulin and Dextran 1 pre-treatment for safe use of Dextran 40/70; research program (facilitates development of safe and effective biological products) OBRR, CBER.

- Information regarding CBER's scientific program is outlined in its Strategic Plan of 2004 and is available to the public on the internet at: http://www.fda.gov/cber/inside/mission.html.
- Closed Discussion Topics: internal research programs in the OBRR, CBER.

- September 29, 2005
  - Open Discussion Topics: new drug application, proposed trade name Exjade (deferasirox) Tablets for Oral Suspension, Novartis Pharmaceutical Corporation, proposed for the indication of the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis); overview of the research programs in the Laboratory of Hemostasis and the Laboratory of Plasma Derivatives, Division of Hematology, OBRR, CBER.
  - Closed Discussion Topics: review of internal research programs in the Division of Hematology, OBRR, CBER; the report from the laboratory site visit of February 25, 2005.

Cellular, Tissue and Gene Therapies Advisory Committee
(Formerly Biological Response Modifiers Advisory Committee)

- March 3-4, 2005
  - Open Discussion Topics: cellular therapies for repair and regeneration of joint surfaces; safety issues related to retroviral vector-mediated tumorigenesis in gene transfer clinical trials.

- May 20, 2005
  - Committee Update: individual research programs in the Division of Therapeutic Proteins, Center for Drug Evaluation and Research (CDER).
  - Closed Discussion Topics: a review of individual FDA research programs.

- July 29, 2005
  - Open Discussion Topics: none
  - Closed Discussion Topics: individual FDA research programs.

- September 29, 2005
  - Open Discussion Topics: presentations about the research program (supporting the regulatory mission and facilitate development of safe and effective biological products) at the Office of Cellular, Tissue and Gene Therapies (OCTGT), CBER.
  - Closed Discussion Topics: internal research programs in the OCTGT, CBER.

Transmissible Spongiform Encephalopathies Advisory Committee

- October 14, 2004
  - Committee Updates: USDA-licensed tests for the diagnosis of bovine spongiform encephalopathy (BSE) and other transmissible spongiform encephalopathies (TSE); review of the worldwide BSE situation; new FDA/CFSAN BSE-food safety rules; labeling claims for TSE clearance studies for plasma derivative products.
  - Open Discussion: presumptive transfusion transmissions of variant Creutzfeldt Jakob Disease (vCJD) and current FDA-recommended safeguards.

- February 8, 2005
  - Open Discussion Topics: risk assessments for potential exposure to the vCJD agent in plasma products; possible vCJD risk from investigational coagulation Factor XI manufactured in the 1990's from plasma of donors residing in the United Kingdom; potential deferral of blood and plasma donors for history of transfusion in France and other European countries.

Vaccines and Related Biological Products Advisory Committee

- February 16-17, 2005
  - Open Discussion Topics: selection of strains to be included in the influenza virus vaccine for the 2005-2006 season.
  - Committee Updates: FDA Critical Path Initiative and research programs in CBER.
  - Closed Discussion Topics: individual research programs in CBER; update on a product under review.

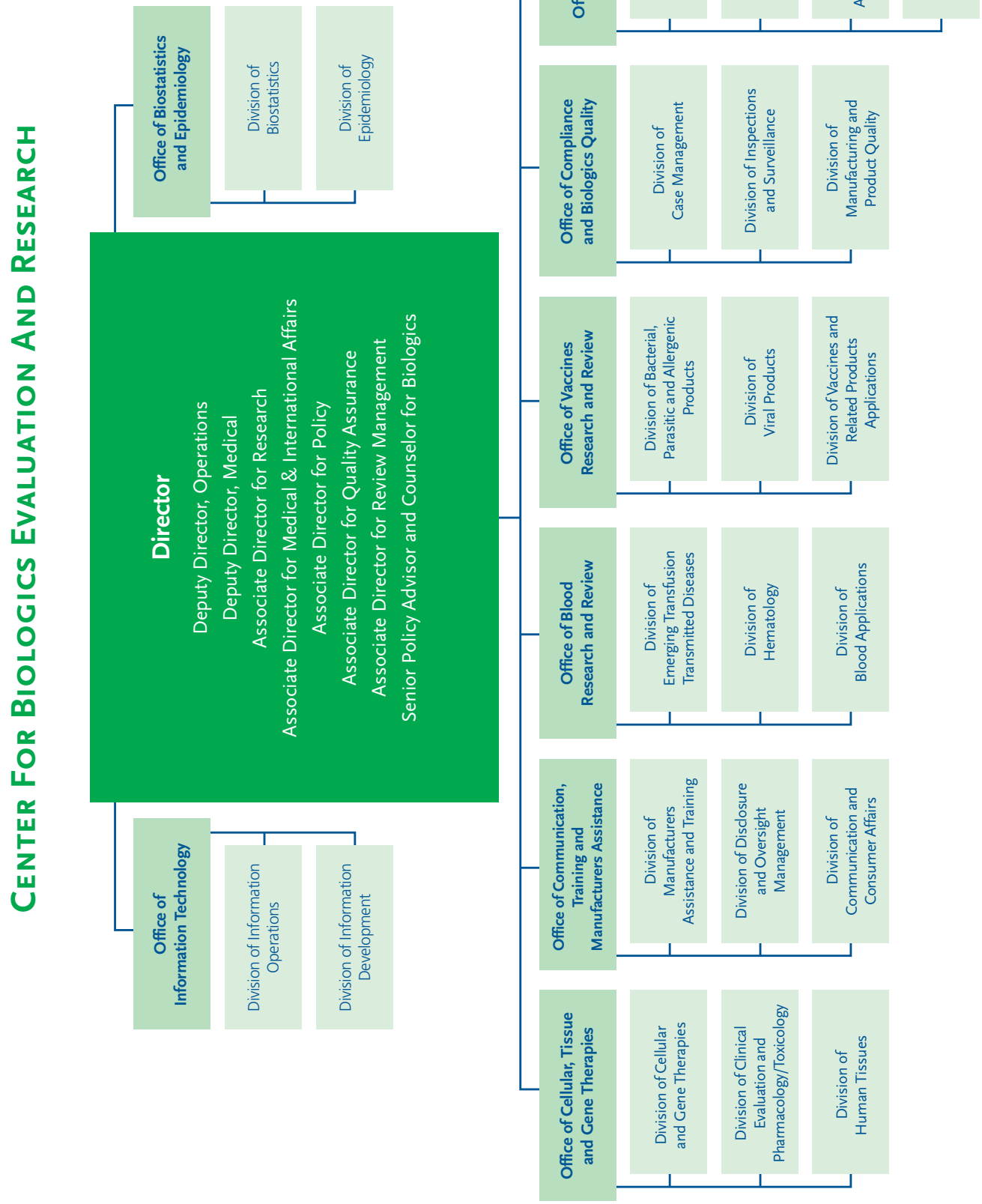
- March 15, 2005
  - Open Discussion Topics: review safety and immunogenicity for two Tetanus Toxoid, Reduced Diphtheria Toxoid and Accellular Pertussis Vaccine, Adsorbed (Tdap) vaccines for individuals 10-18 years of age—Boostrix™ manufactured by GlaxoSmithKline Biologicals and ADACEL™ manufactured by Aventis Pasteur Ltd.

- September 22, 2005
  - Open Discussion Topics: the April 18-19, 2005 site visit of the intramural research programs of the Laboratory of Retroviruses and the Laboratory of Immunoregulation, Division of Viral Products; and the June 16, 2005 site visit of the Laboratory of Respiratory & Special Pathogens and the Laboratory of Methods Development & Quality Control, Division of Bacterial Parasitic & Allergenic Products, Office of Vaccines Research and Review (OVRR), CBER.
  - Closed Discussion Topics: site visit reports from the April 18-19, 2005 Laboratory of Retroviruses and Laboratory of Immunoregulation; and the June 16, 2005 Laboratory of Respiratory and Special Pathogens and Laboratory of Methods Development & Quality Control, OVRR, CBER.

CBER 2005 meeting transcripts may be viewed at:
http://www.fda.gov/ohrms/dockets/ac/cber05.html

Meetings are closed: to permit discussion where disclosure would constitute a clearly unwarranted invasion of personal privacy (5 U.S.C. 552b(c) (6)); to permit discussion and review of trade secret and/or confidential information (5 U.S.C. 552b(c) (4)).

APPENDIX E (Organizational Chart)



U.S. Department of Health and Human Services
Food and Drug Administration